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60/140,345 21 June 1999 (21.06.1999) US
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(54) Title: A METHOD FOR THE PROPHYLAXIS AND/OR TREATMENT OF MEDICAL DISORDERS

(57) Abstract: The present invention relates generally to a method for the prophylaxis and/or treatment of skin disorders, and in particular proliferative and/or inflammatory skin disorders, and to genetic molecules useful for same. The present invention is particularly directed to genetic molecules capable of modulating growth factor interaction with its receptor on epidermal keratinocytes to inhibit, reduce or otherwise decrease stimulation of this layer of cells. The present invention contemplates, in a most preferred embodiment, a method for the prophylaxis and/or treatment of psoriasis.

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## **A METHOD FOR THE PROPHYLAXIS AND/OR TREATMENT OF MEDICAL DISORDERS**

### **5 FIELD OF THE INVENTION**

The present invention relates generally to a method for the prophylaxis and/or treatment of medical disorders, and in particular proliferative and/or inflammatory skin disorders, and to genetic molecules useful for same. The present invention is particularly directed to genetic  
10 molecules capable of modulating growth factor interaction with its receptor on cells such as epidermal keratinocytes to inhibit, reduce or otherwise decrease stimulation of this layer of cells. The present invention contemplates, in a particularly preferred embodiment, a method for the prophylaxis and/or treatment of psoriasis or neovascularization conditions such as neovascularization of the retina. The present invention is further directed to the subject genetic  
15 molecules in adjunctive therapy for epidermal hyperplasia, such as in combination with UV treatment, and to facilitate apoptosis of cancer cells and in particular cancer cells comprising keratinocytes.

### **BACKGROUND OF THE INVENTION**

20

Bibliographic details of the publications numerically referred to in this specification are collected at the end of the description.

The reference to any prior art in this specification is not, and should not be taken as, an  
25 acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia or any other country.

Psoriasis and other similar conditions are common and often distressing proliferative and/or inflammatory skin disorders affecting or having the potential to affect a significant proportion  
30 of the population. The condition arises from over proliferation of basal keratinocytes in the epidermal layer of the skin associated with inflammation in the underlying dermis. Whilst a

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range of treatments have been developed, none is completely effective and free of adverse side effects. Although the underlying cause of psoriasis remains elusive, there is some consensus of opinion that the condition arises at least in part from over expression of local growth factors and their interaction with their receptors supporting keratinocyte proliferation *via* keratinocyte  
5 receptors which appear to be more abundant during psoriasis.

One important group of growth factors are the dermally-derived insulin-like growth factors (IGFs) which support keratinocyte proliferation. In particular, IGF-I and IGF-II are ubiquitous peptides each with potent mitogenic effects on a broad range of cells. Molecules of the IGF type  
10 are also known as "progression factors" promoting "competent" cells through DNA synthesis. The IGFs act through a common receptor known as the Type I or IGF-I receptor, which is tyrosine kinase linked. They are synthesised in mesenchymal tissues, including the dermis, and act on adjacent cells of mesodermal, endodermal or ectodermal origin. The regulation of their synthesis involves growth hormone (GH) in the liver, but is poorly defined in most tissues [1].

15 Particular proteins, referred to as IGF binding proteins (IGFBPs), appear to be involved in autocrine/paracrine regulation of tissue IGF availability [2]. Six IGFBPs have so far been identified. The exact effects of the IGFBPs is not clear and observed effects *in vitro* have been inhibitory or stimulatory depending on the experimental method employed [3]. There is some  
20 evidence, however, that certain IGFBPs are involved in targeting IGF-I to its cell surface receptor.

Skin, comprising epidermis and underlying dermis, has GH receptors on dermal fibroblasts [4]. Fibroblasts synthesize IGF-I as well as IGFBPs-3, -4, -5 and -6 [5] which may be involved in  
25 targeting IGF-I to adjacent cells as well as to the overlying epidermis. The major epidermal cell type, the keratinocyte, does not synthesize IGF-I, but possesses IGF-I receptors and is responsive to IGF-I [6].

It is apparent, therefore, that IGF-I and other growth promoting molecules, are responsible for  
30 or at least participate in a range of skin cell activities. In accordance with the present invention, the inventors have established that aberrations in the normal functioning of these molecules or

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aberrations in their interaction with their receptors is an important factor in a variety of medical disorders such as proliferative and/or inflammatory skin disorders. It is proposed, therefore, to target these molecules or other molecules which facilitate their functioning or interaction with their receptors to thereby ameliorate the effects of aberrant activity during or leading to skin  
5 disease conditions and other medical conditions such as those involving neovascularization. Furthermore, these molecules may also be used to facilitate apoptosis of target cells and may be useful as adjunctive therapy for epidermal hyperplasia.

### SUMMARY OF THE INVENTION

10

Nucleotide and amino acid sequences are referred to by a sequence identifier, i.e. (<400>1), (<400>2), etc. A sequence listing is provided after the claims.

Throughout this specification, unless the context requires otherwise, the word "comprise", or  
15 variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Accordingly, one aspect of the present invention contemplates a method for ameliorating the  
20 effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved in the said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing a growth factor mediated cell proliferation and/or  
25 inflammation and/or other medical disorder.

According to this preferred embodiment, there is provided a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin  
30 capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof



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capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation and/or other medical disorder.

According to this embodiment, there is provided a method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

10

According to this embodiment, there is provided in a particularly preferred aspect a ribozyme comprising a hybridising region and a catalytic region wherein the hybridising region is capable of hybridising to at least part of a target mRNA sequence transcribed from a genomic gene corresponding to <400>1 or <400>2 wherein said catalytic domain is capable of cleaving said target mRNA sequence to reduce or inhibit IGF-I mediated cell proliferation and/or inflammation and/or other medical disorders.

Yet another aspect of the present invention contemplates co-suppression to reduce expression or to inhibit translation of an endogenous gene encoding, for example, IGF-I, its receptor, or IGFBPs such as IGFBP-2 and/or -3. In co-suppression, a second copy of an endogenous gene or a substantially similar copy or analogue of an endogenous gene is introduced into a cell following topical administration. As with antisense molecules, nucleic acid molecules defining a ribozyme or nucleic acid molecules useful in co-suppression may first be protected such as by using a nonionic backbone.

25

Another aspect of the present invention contemplates a pharmaceutical composition for topical administration which comprises a nucleic acid molecule capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation such as psoriasis and one or more pharmaceutically acceptable carriers and/or diluents.

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- 5 -

Yet another aspect of the present invention contemplates the use of a nucleic acid molecule in the manufacture of a medicament for the treatment of proliferative and/or inflammatory skin disorders or other medical disorders mediated by a growth factor.

- 5 Still a further aspect of the present invention contemplates an agent comprising a nucleic acid molecule as hereinbefore defined useful in the treatment of proliferative and/or inflammatory skin disorders, such as psoriasis or other medical disorder..

The present invention further contemplates the use of the genetic molecules and in particular  
10 the antisense molecules to inhibit the anti-apoptotic activity of IGF-I receptor.

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## BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a representation of the nucleotide sequence of IGFBP-2.

```

LOCUS      HSIGFBP2      1433 bp      RNA      PRI      31-JAN-1990
5 DEFINITION Human mRNA for insulin-like growth factor binding protein (IGFBP-2)
ACCESSION  X16302
KEYWORDS   insulin-like growth factor binding protein.
SOURCE      human
ORGANISM    Homo sapiens
10          Eukaryota; Animalia; Metazoa; Chordata; Vertebrata; Mammalia;
          Theria; Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.
REFERENCE   1 (bases 1 to 1433)
AUTHORS     Binkert,C., Landwehr,J., Mary,J.L., Schwander,J. and Heinrich,G.
TITLE        Cloning, sequence analysis and expression of a cDNA encoding a
15          novel insulin-like growth factor binding protein (IGFBP-2)
JOURNAL      EMBO J. 8, 2497-2502 (1989)
STANDARD     full automatic
COMMENT      NCBI gi: 33009
FEATURES
20          Location/Qualifiers
          source          1. .1433
                          /organism="Homo sapiens"
                          /dev_stage="fetal"
                          /tissue_type="liver"
          misc_feature    1416. .1420
25          /note="pot. polyadenylation signal"
          polyA_site      1433
                          /note="polyadenylation site"
          CDS              118. .1104
                          /note="precursor polypeptide; (AA -39 to 289); NCBI gi:
30          33010."
                          /codon_start=1
                          /translation="MLPRVGC PALPLPPPPLLPLPLLLLLLGASGGGGGARA EVLFR
CPPCTPERLAACGPPPVAPPAVA AVAGGARMPCAELVREPGCGCCSV CARLEGEACG
VYTPRCGQLRCYPHPGSELPLQALVMGEGTCEKRRDAEY GASPEQVADNGDDHSEGG
35          LVENHVDSTMNMLGGGGSAGRKPLKSGMKELAVFREKVTEQHRQMGKGKHHLGLEEP
KKLRPPPARTPCQQLDQVLERISTMRLPDERGPLEHLYSLHIPNCDKHGLYNLKQCK
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(<400>21)
          CDS              118. .234
40          /note="signal peptide; (AA -39 to -1); NCBI gi: 33011."
                          /codon_start=1
                          /translation="MLPRVGC PALPLPPPPLLPLPLLLLLLGASGGGGGARA"
(<400>22)
          CDS              235. .1101
45          /note="mature IGFBP-2; (AA 1 to 289); NCBI gi: 33012."
                          /codon_start=1
                          /translation="EVLFRCPPCTPERLAACGPPPVAPPAVA AVAGGARMPCAELVR
EPGCGCCSV CARLEGEACGVYTPRCGQLRCYPHPGSELPLQALVMGEGTCEKRRDAE
YGASPEQVADNGDDHSEGG LVENHVDSTMNMLGGGGSAGRKPLKSGMKELAVFREKVT
50          EQHRQMGKGKHHLGLEEPKKLRPPPARTPCQQLDQVLERISTMRLPDERGPLEHLY
SLHIPNCDKHGLYNLKQCKMSLNGQRGECWCVNPN TGKLIQGAPTIRGDPECHLFYNE
QQEACGVHTQRMQ" (<400>23)
BASE COUNT  239 a 466 c 501 g 227 t
ORIGIN
55

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HSIGFBP2 Length: 1433 May 11, 1994 10:06 Type: N Check: 6232 ..

Figure 2 is a representation of the nucleotide sequence of IGFBP-3.

5  
LOCUS HUMGFIBPA 2474 bp ss-mRNA PRI 15-JUN-1990  
DEFINITION Human growth hormone-dependent insulin-like growth factor-binding protein mRNA, complete cds.  
ACCESSION M31159  
10 KEYWORDS insulin-like growth factor binding protein.  
SOURCE Human plasma, cDNA to mRNA, clone BP-53.  
ORGANISM Homo sapiens  
Eukaryota; Animalia; Chordata; Vertebrata; Mammalia; Theria; Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.  
15 REFERENCE 1 (bases 1 to 2474)  
AUTHORS Wood,W.I., Cachianes,G., Henzel,W.J., Winslow,G.A., Spencer,S.A., Hellmiss,R., Martin,J.L. and Baxter,R.C.  
TITLE Cloning and expression of the growth hormone-dependent insulin-like growth factor-binding protein  
20 JOURNAL Mol. Endocrinol. 2, 1176-1185 (1988)  
STANDARD full automatic  
COMMENT NCBI gi: 183115  
FEATURES Location/Qualifiers  
mRNA <1..2474  
25 /note="GFIBP mRNA"  
CDS 110..985  
/feature="IGFBP1"  
/feature="insulin-like growth factor-binding protein; NCBI gi: 183116."  
30 /codon\_start=1  
/translation="MQRARPTLWAAALTLLVLLRGPPVARAGASSGGLGPVVRCEPCD  
ARALAQCAPPAPVCAELVREPGCGCCLTCALSEGQPCGIYTERCGSLRCQPSPEAR  
PLQALLDGRGLCVNASAVSRLRAYLLPAPPAPGNASESEEDRSAGSVESPSVSTHRV  
SDPKFHLHLSKIIIIKKGHAKDSQRYKVDYESQSTDTQNFSSSESKRETEYGPCRREME  
35 DTLNHLKFLNVLSPRGVHIPNCDKKGFKKQCRPSKGRKRGFCWCVDKYGQPLPGYT  
TKGKEDVHCYSMQSK" (<400>24>)  
source 1..2474  
/organism="Homo sapiens"  
BASE COUNT 597 a 646 c 651 g 580 t  
40 ORIGIN

HUMGFIBPA Length: 2474 May 11, 1994 10:00 Type: N Check: 9946 ..

45 Figure 3 is a representation of the nucleotide sequence of IGF-1-receptor.

LOCUS HSIGFIRR 4989 bp RNA PRI 28-MAR-1991  
DEFINITION Human mRNA for insulin-like growth factor I receptor  
ACCESSION X04434 M24599  
50 KEYWORDS glycoprotein; insulin receptor;  
insulin-like growth factor I receptor; membrane glycoprotein;  
receptor; tyrosine kinase.  
SOURCE human

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ORGANISM Homo sapiens  
 Eukaryota; Animalia; Metazoa; Chordata; Vertebrata; Mammalia;  
 Theria; Eutheria; Primates; Haplorhini; Catarrhini; Hominidae.

REFERENCE 1 (bases 1 to 4989)

5 AUTHORS Ullrich,A., Gray,A., Tam,A.W., Yang-Feng,T., Tsubokawa,M.,  
 Collins,C., Henzel,W., Bon,T.L., Kathuria,S., Chen,E., Jakobs,S.,  
 Francke,U., Ramachandran,J. and Fujita-Yamaguchi,Y.

TITLE Insulin-like growth factor I receptor primary structure: comparison  
 with insulin receptor suggests structural dererminants that define  
 10 functional specificity

JOURNAL EMBO J. 5, 2503-2512 (1986)

STANDARD full automatic

COMMENT NCBI gi: 33058

FEATURES Location/Qualifiers

15 source 1. .4989  
 /organism="Homo sapiens"  
 /tissue\_type="placenta"  
 /clone\_lib="(lamda)gt10"  
 /clone="(lambda)IGF-1-R.85, (lambda)IGF-1-R.76"

20 sig\_peptide 32. .121  
 mat\_peptide 122. .4132  
 /note="IGF-I receptor"

misc\_feature 122. .2251  
 /note="alpha-subunit (AA 1 - 710)"

25 misc\_feature 182. .190  
 /note="pot.N-linked glycosylation site (AA 21 - 23)"

misc\_feature 335. .343  
 /note="pot.N-linked glycostlation site (AA 72 - 74)"

30 misc\_feature 434. .442  
 /note="pot.N-linked glycostlation site (AA 105 - 107)"

misc\_feature 761. .769  
 /note="pot.N-linked glycostlation site (AA 214 - 216)"

misc\_feature 971. .979  
 /note="pot.N-linked glycostlation site (AA 284 - 286)"

35 misc\_feature 1280. .1288  
 /note="pot.N-linked glycostlation site (AA 387 - 389)"

misc\_feature 1343. .1351  
 /note="pot.N-linked glycosylation site (AA 408 - 410)"

40 misc\_feature 1631. .1639  
 /note="pot.N-linked glycostlation site (AA 504 - 506)"

misc\_feature 1850. .1858  
 /note="pot.N-linked glycosylation site (AA 577 - 579)"

misc\_feature 1895. .1903  
 /note="pot.N-linked glycosylation site (AA 592 - 594)"

45 misc\_feature 1949. .1957  
 /note="pot.N-linked glycosylation site (AA 610 - 612)"

misc\_feature 2240. .2251  
 /note="putative proreceptor processing site (AA 707 -  
 710)"

50 misc\_feature 2252. .4132  
 /note="beta-subunit (AA 711 - 1337)"

misc\_feature 2270. .2278  
 /note="pot.N-linked glycosylation site (AA 717 - 719]"

misc\_feature 2297. .2305  
 /note="pot.N-linked glycosylation site (AA 726 - 728)"

55 misc\_feature 2321. .2329  
 /note="pot.N-linked glycosylation site (AA 734 - 736)"

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                        /note="pot.N-linked glycosylation site (AA 883 - 885)"
5    misc_feature      2837. .2908
                        /note="transmembrane region (AA 906 - 929)"
    misc_feature      2918. .2926
                        /note="pot.N-linked glycosylation site (AA 933 - 935)"
    misc_feature      3047. .3049
10   misc_feature      3053. .3055
                        /note="pot.ATP binding site (AA 976)"
    misc_feature      3062. .3064
                        /note="pot.ATP binding site (AA 978)"
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                        /note="pot.ATP binding site (AA 981)"
15   misc_feature      3128. .3130
                        /note="pot.ATP binding site (AA 1003)"
    CDS                32. .4132
                        /product="IGF-I receptor"
                        /note="50 stops when translation attempted, frame 1, code
20   0"
BASE COUNT      1216 a   1371 c   1320 g   1082 t
ORIGIN

```

HSIGFIRR Length: 4989 May 11, 1994 12:10 Type: N Check: 133 ..

25

**Figure 4A** is a photographic representation of a Western ligand blot of HaCaT conditioned medium showing IGFBP-3 secreted in 24 hours after 7 day treatment with phosphorothioate oligonucleotides (BP3AS2, BP3AS3 and BP3S) at 0.5 $\mu$ M and 5 $\mu$ M;

30 \* no oligonucleotide added.

**Figure 4B** is a graphical representation of a scanning imaging desitometry of Western ligand blot (Figure 4A), showing relative band intensities of IGFBP-3 and the 24kDa IGFBP-4 after treatment with phosphorothioate oligonucleotides;

35 \* no oligonucleotide added.

**Figure 5A** is a photographic representation of a Western ligand blot of HaCaT conditioned medium showing IGFBP-3 secreted in 24 hours after 7 day treatment with phosphorothioate oligonucleotide BP3AS2 at 0.5 $\mu$ M compared with several control oligonucleotides at 0.5 $\mu$ M.

40 (a) oligonucleotide BP3AS2NS; (b) oligonucleotide BP3AS4; (c) oligonucleotide BP3AS4NS; and (untreated), no oligonucleotide added.

- 10 -

**Figure 5B** is a graphical representation of a scanning imaging densitometry of Western ligand blot (Figure 5A), showing relative band intensities of IGFBP-3 after treatment with phosphorothioate oligonucleotides as in Figure 5A, showing IGFBP-3 band intensities expressed as a percentage of the average band intensity from conditioned medium of cells not  
5 treated with oligonucleotide.

**Figure 6** is a graphical representation showing inhibition of IGF-I binding by antisense oligonucleotides to IGF-I receptor. IGFR.AS: antisense; IGFR.S: sense.

10 **Figure 7** is a graphical representation showing inhibition of IGFBP-3 production in culture medium following initial treatment with antisense oligonucleotides once daily over a 2 day period.

**Figure 8** is a graphical representation showing optimization of IGFBP-3 antisense  
15 oligonucleotide concentration as determined by relative IGFBP-3 concentration in culture medium.

**Figure 9** is a diagrammatic representation of a map of IGF-1 Receptor mRNA and position of target ODNs.

20

**Figure 10** is a photographic representation showing Lipid-mediated uptake of oligonucleotide in keratinocytes. HaCaT keratinocytes were incubated for 24 hours in medium (DMEM plus 10% v/v FCS) containing fluorescently labelled ODN (R451, 30 nM) and cytofectin GSV (2  $\mu$ g/ml). The cells were then transferred to ODN-free medium and  
25 fluorescence microscopy (a) and phase contrast (b) images of the cells were obtained.

**Figure 11** is a graphical representation of uptake (A) and toxicity (B) of ODN/lipid complexes in keratinocytes. Confluence HaCaT keratinocytes were incubated in DMEM containing fluorescently labelled ODN (R451) plus liposome over 120 hours, viewed using fluoresce  
30 microscopy and trypan blue stained and counted.

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**Figure 12** is a graphical representation of an IGF-1 Receptor mRNA in ODN treated (30nM) HaCaT cells (2 $\mu$ g/ml GSV). HaCaT keratinocytes were treated for 96 hours with C-5 propynyl, dU, dC ODNs complexed with cytofectin GSV. Cells were treated with ODNs complementary to the human IGF-I receptor mRNA (27, 32, 74 and 78), 2 randomised  
 5 sequence ODNs (R451) and R766), liposome alone (GSV) or were left untreated (UT). Total RNA was isolated then analysed for IGF-I receptor mRNA and GAPDH mRNA levels by RNase Protection and PhosphorImager quantitation.

(A) Electrophoretic analysis of IGF-I receptor and GAPDH mRNA fragments after RNase  
 10 Protection. Molecular weight markers are shown on the right hand side. Full length probe is shown on the left hand side (G-probe and I-probe). GAPDH protected fragments (G) are seen at 316 bases and IGF-I receptor protected fragments (I) are seen at 276 bases.

(B) Relative level of IGF-I receptor mRNA following each treatment is shown.  
 15

**Figure 13** is a graphical representation of an IGF-1 receptor mRNA in ODN treated (30nM) HaCaT cells (2 $\mu$ g/ml GSV). Summary of IGF-I receptor ODN screening data. HaCaT keratinocytes were treated for 96 hours with C-5 propynyl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGF-I receptor mRNA and  
 20 GAPDH mRNA levels by RNase protection and phosphorImager quantitation. Relative level of IGF-I receptor mRNA is shown after treatment with ODNs complementary to the human IGF-I receptor mRNA, 4 randomised sequence ODNs and liposome alone. (26-86=IGF-I receptor ODNs; R1, R4, R7 and R9 = randomised ODNs (R1=R121, R4=R451, R7=R766, R9=R961); GSV=liposome alone; UT=untreated). \*indicates a significant difference in  
 25 relative IGF-I receptor mRNA from GSV treated cells (n=4-10, p<0.05).

**Figure 14** is a graphical representation of the effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes. HaCaT cells were grown to confluence in 24-well plates in DMEM containing 10% v/v FCS. Oligodeoxynucleotide (ODN) and Cytofectin  
 30 GSV (GSV, Glen Research) were mixed together in serum-free DMEM, incubated at room



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temperature for 10 minutes before being diluted ten-fold in medium and placed on the cells. Cells were incubated for 72 hours with 30 nM random sequence or antisense ODN and 2  $\mu\text{g/ml}$  GSV or with GSV alone in DMEM containing 10% v/v FCS with solutions replaced every 24 hours. This was followed by incubation with ODN/GSV in serum-free DMEM for 5 48 hours. All incubations were performed at 37°C. Wells were washed twice with 1 ml cold PBS. Serum-free DMEM containing  $10^{-10}\text{M}$   $^{125}\text{I}$ -IGF-I was added with or without the IGF-I analogue, des (1-3) IGF-I, at  $10^{-10}\text{M}$  to  $10^{-7}\text{M}$ . Cells were incubated at 4°C for 17 hours with gentle shaking then washed three times with 1 ml cold PBS and lysed in 250  $\mu\text{l}$  0.5M NaOH/0.1% v/v Triton X-100 at room temperature for 4 hours. Specific binding of the 10 solubilised cell extract was measured using a  $\gamma$  counter.

**Figure 15** is a graphical representation of the effect of antisense oligonucleotides on IGF-1 receptor levels on the surface of keratinocytes.

15 **Figure 16** is a photographic representation of H & E stained sections of (A) psoriatic skin biopsy prior to grafting and (B) 49 day old psoriatic skin graft using skin from the same donor.

**Figure 17** is a photographic representation of uptake of oligonucleotide after intradermal 20 injection into psoriatic skin graft on a nude mouse. Psoriatic skin graft was intradermally injected with ODN (R451, 50  $\mu\text{l}$ , 10  $\mu\text{M}$ ). The graft was removed and sectioned after 24 hours, then viewed using confocal microscopy.

25 **Figure 18(a)** is a photographic representation of Pregraft, Donor JH, Donor JH, PBS treated, 50 $\mu\text{l}$ , Donor JH, #50 treated, 50 $\mu\text{l}$ , 10 $\mu\text{M}$ .

**Figure 18(b)** is a photographic representation of Donor LB, pregraft, Donor LB, PBS treated (50 $\mu\text{l}$ ), Donor LB, #74 treated (50 $\mu\text{l}$ , 10 $\mu\text{M}$ ).

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**Figure 18(c)** is a photographic representation of Donor PW, pregraft, Donor PW, R451 treated (50 $\mu$ l, 10 $\mu$ M), Donor LB, #74 treated (50 $\mu$ l, 10 $\mu$ M).

**Figure 18(d)** is a photographic representation of Donor GM, pregraft, Donor GB, R451  
5 treated (50 $\mu$ l, 10 $\mu$ M), Donor GM, #27 treated (50 $\mu$ l, 10 $\mu$ M).

**Figure 19(a)** is a photographic representation showing Donor JH pregraft, Donor JH PBS treated 50 $\mu$ l, Donor JH #50 treated 50 $\mu$ l, 10 $\mu$ M.

10 **Figure 19(b)** is a photographic representation Donor LB pregraft, Donor LB PBS treated 50 $\mu$ l, Donor LB #74 treated 50 $\mu$ l, 10 $\mu$ M.

**Figure 19(c)** is a photographic representation showing Donor PW pregraft, Donor PW R451 treated 50 $\mu$ l, 10 $\mu$ M, Donor PW #74 treated 50 $\mu$ l, 10 $\mu$ M.

15

**Figure 19(d)** is a photographic representation showing Donor GM pregraft, Donor GM R451 treated 50 $\mu$ l, 10 $\mu$ M, Donor #27 treated 50 $\mu$ l, 10 $\mu$ M.

**Figure 20** is a graphical representation showing suppression of psoriasis after treatment with  
20 oligonucleotide (quantification). Oligonucleotide (50  $\mu$ l, 10 $\mu$ M) was injected every two days for 20 days, as were control treatments. Skin thickness was measured by removing the skin and using computer software (MCID analysis) to measure the exact thickness of each graft. N=3-4 for each treatment. \*indicates a significant difference from the pregraft value (ANOVA, P<0.05)

25

**Figure 21** is a photographic representation of  $\alpha$ hKi-67 immunobiological binding.

**Figure 22** is a photographic representation showing penetration of oligonucleotide into human skin after topical treatment. Fluorescently labelled oligonucleotide (10  $\mu$ M R451) was

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applied topically after formulation with cytofectin GSV (10  $\mu$ g/ml) and viewed using confocal microscopy.

**Figure 23** is a photographic representation showing penetration of oligonucleotide into human skin after application of topical gel formation. Fluorescently labelled oligonucleotide (10  $\mu$ M R451) was applied topically after complexing with cytofectin GSV (10  $\mu$ g/ml) and formulation into 3% methylcellulose gel. Image was obtained using confocal microscopy.

**Figure 24** is a graphical representation showing IGFBP-3 mRNA.

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**Figure 25(a)** is a graphical representation showing IGFBP-3 mRNA in AON treated (100nM) HaCaT cells (2 $\mu$ g/ml GSV).

**Figure 25(b)** is a graphical representation showing IGFBP-3 mRNA levels of AON treated (100nm) HaCaT cells (2 $\mu$ g/ml GSV).

**Figure 25(c)** is a graphical representation showing IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2 $\mu$ g/ml GSV).

20 **Figure 25(d)** is a graphical representation showing IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2 $\mu$ g/ml GSV).

**Figure 26(a)** is a graphical representation showing IGFBP-3 mRNA in ODN treated (30nM) HaCaT cells (2 $\mu$ g/ml). HaCaT keratinocytes were treated for 51 hours with C-5 propynl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGFBP-3 mRNA and GAPDH mRNA levels by Northern analysis and phosphorimager quantitation. Relative level of IGFBP-3 mRNA is shown after treatment with ODNs complementary to the human IGFBP-3 mRNA, 4 randomised sequence ODNs and liposome alone. (1-24=IGFBP-3 ODNs; R1, R4, R7 and R9=randomised ODNs (R1=R121, R4=R451, R7=R766, R9 R961); GS=liposome alone; UT=untreated). \*indicates a significant different in relative

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IGFBP-3 mRNA from GSV treated cells (n= 5-8,  $p < 0.01$ ), \*\*indicates a significant difference in relative IGFBP-3 mRNA from GSV treated cells (n= 5-8,  $p < 0.05$ ).

**Figure 26(b)** is a graphical representation showing IGFBP-3 mRNA in ODN treated (100nM) HaCaT cells ( $2\mu\text{g/ml}$  GSV). HaCaT keratinocytes were treated for 51 hours with C-5 propynl, dU, dC ODNs complexed with cytofectin GSV. Total RNA was isolated then analysed for IGFBP-3 mRNA and GAPDH mRNA levels by Northern analysis and phosphorimager quantitation. Relative level of IGFBP-3 mRNA is shown after treatment with ODNs complementary to the human IGFBP-3 mRNA, 4 randomised sequence ODNs and liposome alone. (1-24=IGFBP-3 ODNs; R1, R4, R7 and R9 = randomised ODNs (R1-R121, R4=R451, R7=R766, R9=R961), GS=liposome alone; UT=untreated). \*indicates a significant difference in relative IGFBP-3 mRNA from GSV treated cells (n= 6-8,  $p < 0.01$ ).

**Figure 27** is a representation showing a reduction in IGF-I receptor mRNA in HaCaT cells following treatment with antisense oligonucleotides. Confluent HaCaT cells were treated every 24 h for 4 days with  $2\mu\text{g/ml}$  GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific oligonucleotides (#26 to #86) or random sequence oligonucleotides (R121, R451 and R766). Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA by RNase protection assay. (a). Representative RNase protection assay gel showing IGF-I receptor (*IGFR*) and GAPDH mRNA in untreated or treated HaCaT cells. In this example, a reduction in IGFR band intensity relative to GAPDH can be seen with AON #27 and #78, but not with #32, #74 or the controls (R4, R7, random oligonucleotides R451 and R766, respectively; G, GSV lipid; UT, untreated).

(b) Densitometric quantitation of IGF-I receptor mRNA (normalised to GAPDH mRNA) in HaCaT cells following treatment with IGF-I receptor specific oligonucleotides (solid black), random sequence oligonucleotides (horizontal striped bar) or GSV alone (shaded bar) compared to untreated cells (UT, vertical striped bar). Each oligonucleotide was assayed in duplicate in at least two separate experiments.

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Results are presented as mean  $\pm$  SEM. A one-way ANOVA followed by Tukey's ( $\Delta$ ) test was performed;  $\Delta$  indicates a significant difference between cells treated with IGF-I receptor specific AONs and all of the control treatments ( $p < 0.05$ ).  $n=4$  except for #27 and #32 ( $n=6$ ), #28 and #68 ( $n=3$ ), R766 ( $n=9$ ), and R451, GSV and untreated ( $n=10$ ).

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**Figure 28** is a representation showing a reduction in total cellular IGF-I receptor protein following antisense oligonucleotide treatment. Confluent HaCaT cells were treated every 24 h for 4 days with 2  $\mu$ g/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific AONs (#27, #50 and #64) or the random sequence oligonucleotide, R451. Total cellular protein was isolated and analysed for IGF-I receptor by SDS PAGE followed by western blotting with an antibody specific for the human IGF-I receptor. (a) Duplicate treated cellular extracts showing the IGF-I receptor at the predicted size of 110 kD

(b) Densitometric quantitation of IGF-I receptor protein. Results are presented as mean  $\pm$  SEM of four different experiments each performed in duplicate. A one-way ANOVA followed by a Dunnett's test was performed; \* indicates a significant difference from GSV treated cells ( $p < 0.01$ ). GSV, GSV lipid alone; UT, untreated; R451, random sequence oligonucleotide; 64, 50, 27, IGF-I receptor-specific AONs.

**Figure 29** is a representation showing a reduction in IGF-I receptor numbers on the keratinocyte cell surface after antisense oligonucleotide treatment. HaCaT cells were transfected with IGF-I receptor specific AONs #27 ( $-\Delta-$ ), #50 ( $-x-$ ), #64 ( $---\blacksquare---$ ), a random sequence oligonucleotide R451 ( $-o-$ ), or treated with GSV lipid alone ( $--\square--$ ) every 24 h for four days (untreated cells,  $--*--$ ). Competition binding assays using  $^{125}$ I-IGF-I and the receptor-specific analogue, des(1-3)IGF-I, were performed (inset); plotted values are means  $\pm$  standard error. The mean values were then subjected to Scatchard analysis.

**Figure 30** is a representation showing a reduction in keratinocyte cell number following antisense oligonucleotide treatment. HaCaT cells, initially at 40% confluence, were transfected with the IGF-I receptor specific AON #64, control sequences R451 and 6416, or

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treated with GSV lipid alone every 24 h for 2 days (UT, untreated cells). Cell number was measured in the culture wells using a dye binding assay (Experimental protocol). Results are presented as mean  $\pm$  SD. A one-way ANOVA was performed, followed by a Tukey's multiple comparison test. ▲ indicates a significant difference between cells treated with AON #64 and all of the control treatments ( $p < 0.001$ ).

**Figure 31** is a representation showing a reversal of epidermal hyperplasia in psoriatic human skin grafts on nude mice following intradermal injection with antisense oligonucleotides

10 Grafted psoriasis lesions were injected with IGF-I receptor specific AONs, a random sequence oligonucleotide in PBS, or with PBS alone, every 2 days for 20 days, then analysed histologically. (a) Donor A graft treated with AON #50 showing epidermal thinning compared with pregraft and control (PBS) treated graft, and Donor B graft treated with AON #27 showing epidermal thinning compared with pregraft and control (R451) treated graft. E, 15 epidermis; *Scale bar*, 400  $\mu$ m; all pictures are at the same magnification. (b) Mean epidermal cross-sectional area over the full width of grafts was determined by digital image analysis. Results are presented as mean  $\pm$  SEM. *Shaded bars*, control treatments: R451, random oligonucleotide sequence; *solid bars*, treatments with oligonucleotides that inhibited IGF-I receptor expression in vitro. \* indicates a significant difference from the vehicle treated graft 20 ( $p < 0.01$ ,  $n = 5-7$ ), ++ indicates a significant difference from the random sequence (R451) treated graft ( $p < 0.01$ ,  $n = 5-7$ ). (c) Parakeratosis (*arrow*) was absent in grafts treated with IGF-I receptor AONs (AON #50) but persisted in pregraft and control (PBS) treated graft. *Scale bar*, 100  $\mu$ m.

25 **Figure 32** is a representation showing a reversal of epidermal hyperplasia correlates with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides (a) A psoriasis lesion prior to grafting, and after grafting and treatment with IGF-I receptor specific oligonucleotide #27 (AON #27) or random sequence (R451) was immunostained with antibodies to Ki67 to identify proliferating cells. Proliferating cells are 30 indicated by a dark brown nucleus (arrows). *Scale bar*, 250  $\mu$ m; all pictures are at the same

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magnification. (b) The same lesion prior to grafting and after oligonucleotide treatment as in (a) was subjected to in situ hybridisation with a  $^{35}\text{S}$ -labeled cRNA probe complementary to the human IGF-I receptor mRNA. The presence of IGF-I receptor mRNA is indicated by silver grains (tiny black speckles), which are almost eliminated in the epidermis of the lesion  
5 treated with the IGF-I receptor-specific oligonucleotide #27 (AON #27). Arrows indicate the basal layer of the epidermis with dermis underneath. *Scale bar, 50  $\mu\text{m}$ .*

**Figure 33** is a representation showing a reduction in IGF-I receptor mRNA in HaCaT keratinocytes following treatment with oligonucleotides. HaCaT cell monolayers grown to  
10 90% confluence in DMEM containing 10% v/v fetal calf serum were treated with 24 h for two days with 2  $\mu\text{g}/\text{ml}$  GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA using a commercially available ribonuclease protection assay kit (RPAII, Ambicon Inc, Austin, Texas). Band intensity was quantified using ImageQuant software (Molecular Dynamics, Sunnyvale,  
15 California).

**Figure 34** is a representation showing a reduction in IGF-I receptor protein in HaCaT keratinocytes following treatment with oligonucleotides. HaCaT cell monolayers grown to 90% confluence in DMEM containing 10% v/v fetal calf serum were treated every 24 h for  
20 four days with 2  $\mu\text{g}/\text{ml}$  GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Cells were lysed in a buffer containing 50 mM HEPES, 150 mM NaCl, 10% v/v glycerol, 1% v/v Triton X-100 and 100  $\mu\text{g}/\text{ml}$  aprotinin on ice for 30 mins, then 30  $\mu\text{g}$  of lysate was loaded onto a denaturing 7% w/v polyacrylamide gel followed by transfer onto an Immobilon-P membrane (Millipore, Bedford, Massachusetts). Membranes were incubated with the anti-  
25 IGF-I receptor antibody C20 (Sanra Cruz Biotechnology Inc., Santa Cruz, California, 25 ng/ml in 150 mM NaCl, 10 mM Tris-HCl, pH 7.4, 0.1% v/v Tween 20) for 1 h at room temperature and developed using the Vistra ECF western blotting kit (Amersham, Buckinghamshire, England). Band intensity was quantified using ImageQuant software (Molecular Dynamics, Sunnyvale, California).

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**Figure 35** is a representation showing a reduction in HaCaT keratinocyte cell number following treatment with oligonucleotides. HaCaT cell monolayers grown to 40% confluence in DMEM containing 10% fetal calf serum were treated every 24 h for three days with 2  $\mu\text{g/ml}$  GSV lipid alone (GSV) or complexed with 15 nM oligonucleotide. Cell number was measured every 24 h using the amido black dye binding assay [32].



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## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is predicated in part on the use of molecules and in particular genetic molecules and more particularly antisense molecules to down-regulate a growth factor, its  
5 receptor and/or growth factor expression facilitating sequences.

Accordingly, one aspect of the present invention contemplates a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin  
10 capable of proliferation and/or inflammation or a cell otherwise involved in the said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing a growth factor mediated cell proliferation and/or inflammation and/or other medical disorder.

15 Growth factor mediated cell proliferation and inflammation are also referred to as epidermal hyperplasias and these and other medical disorders may be mediated by any number of molecules such as but not limited to IGF-I, keratinocyte growth factor (KGF), transforming growth factor- $\alpha$  (TGF $\alpha$ ), tumour necrosis factor- $\alpha$  (TNF $\alpha$ ), interleukin-1, -4, -6 and 8 (IL-1, IL-4, IL-6 and IL-8, respectively), basic fibroblast growth factor (bFGF) or a combination  
20 of one or more of the above. The present invention is particularly described and exemplified with reference to IGF-I and its receptor (IGF-I receptor) and to IGF-I facilitating molecules, IGFBPs, since targeting these molecules according to the methods contemplated herein provides the best results to date. This is done, however, with the understanding that the present invention extends to any growth factor or cytokine-like molecule, a receptor thereof  
25 or a facilitating molecule like the IGFBPs involved in skin cell proliferation such as those molecules contemplated above and/or their receptors and/or facilitating molecules therefor.

According to this preferred embodiment, there is provided a method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a  
30 mammal, said method comprising contacting the proliferating and/or inflamed skin or skin

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capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation and/or other medical disorder.

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The present invention is particularly described by psoriasis as the proliferative skin disorder. However, the subject invention extends to a range of proliferative and/or inflammatory skin disorders or epidermal hyperplasias such as but not limited to psoriasis, ichthyosis, pityriasis rubra pilaris ("PRP"), seborrhoea, keloids, keratoses, neoplasias and scleroderma, warts,  
10 benign growths and cancers of the skin. The present invention extends to a range of other disorders such as neovascularization conditions such as but not limited to hyperneovascularization such as neovascularization of the retina, lining of the brain, skin, hyperproliferation of the inside of blood vessels, kidney disease, atherosclerotic disease, hyperplasias of the gut epithelium or growth factor mediated malignancies such as IGF1-  
15 mediated malignancies.

Furthermore, down-regulation of IGF-I receptor is useful as adjunctive therapy for epidermal hyperplasia. In accordance with this aspect of the present invention it is known that IGF-I receptor elicits separate intracellular signals which prevent apoptosis [19]. In keratinocytes,  
20 IGF-I receptor activation has been shown to protect UV-irradiated cells from apoptosis [20]. In another cell type, a number of IGF-I receptors expressed by the cells correlated with tumorigenicity and apoptotic resistance [21]. Consequently, in accordance with the present invention, by inactivating IGF-I receptor on cells such as epidermal keratinocytes will achieve three important outcomes:

25

- (i) Acute epidermal hyperplasia following UV has been suggested to increase the risk of keratinocyte carcinogenic transformation [22]. By reducing IGF-I receptor expression in the epidermis, the incidence of epidermal hyperplasia following UV exposure is likely to be reduced leading to an overall acceleration in normalization of the lesion  
30 and reduced carcinogenic risk.

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- (ii) Inhibition of anti-apoptotic action of IGF-I receptor will enhance the reversal of epidermal thickening and accelerate normalization of differentiation. Topical or injected IGF-I receptor antisense as adjunctive treatment will increase apoptosis in the epidermal layer thereby enhancing the reduction in acanthosis observed in UV treatments.
- (iii) Survival of keratinocytes, ie. those which evade apoptosis is likely to occur when cells have damaged DNA. Such mutations may be in the tumor suppressor region. Consequently, the use of antisense therapy will result in less frequent selection of mutated keratinocytes and therefore reduced incidence of basal cell carcinomas and squamous.

According to this embodiment, there is provided a method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

The UV treatment and nucleic acid molecule or its chemical analogue may be administered in any order or may be done simultaneously. This method is particularly useful in treating psoriasis by combination of UV and antisense therapy. Preferably the antisense therapy is directed to the IGF-I receptor.

In a preferred embodiment, the present invention is directed to a method for ameliorating the effects of psoriasis or other medical disorder, said method comprising contacting proliferating skin or skin capable of proliferation or cells associated with said disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation or ameliorating the medical disorder.

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The present invention extends to any mammal such as but not limited to humans, livestock animals (e.g. horses, sheep, cows, goats, pigs, donkeys), laboratory test animals (e.g. rabbits, mice, guinea pigs), companion animals (e.g. cats, dogs) and captive wild animals. However, the instant invention is particularly directed to proliferative and/or inflammatory skin disorders such as psoriasis in humans as well as medical disorders contemplated above.

The aspects of the subject invention instantly contemplated are particularly directed to the topical application of one or more suitable nucleic molecules capable of inhibiting, reducing or otherwise interfering with IGF-mediated cell proliferation and/or inflammation. More particularly, the nucleic acid molecule targets IGF-I interaction with its receptor. Conveniently, therefore, the nucleic acid molecule is an antagonist of IGF-I interaction with its receptor. Most conveniently, the nucleic acid molecule antagonist is an antisense molecule to the IGF-I receptor, to IGF-I itself or to a molecule capable of facilitating IGF-I interaction with its receptor such as but not limited to an IGFBP.

15

Insofar as the invention relates to IGFBPs, the preferred molecules are IGFBP-2, -3, -4, -5 and -6. The most preferred molecules are IGFBP-2 and IGFBP-3.

The nucleotide sequences of IGFBP-2 and IGFBP-3 are set forth in Figures 1 (<400>1) and 2 (<400>2), respectively. According to a particularly preferred aspect of the present invention, there is provided a nucleic acid molecule comprising at least about ten nucleotides capable of hybridising to, forming a heteroduplex or otherwise interacting with an mRNA molecule directed from a gene corresponding to a genomic form of <400>1 and/or <400>2 and which thereby reduces or inhibits translation of said mRNA molecule. Preferably, the nucleic acid molecule is at least about 15 nucleotides in length and more preferably at least about 20-25 nucleotides in length. However, the instant invention extends to any length nucleic acid molecule including a molecule of 100-200 nucleotides in length to correspond to the full length of or near full length of the subject genes.

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The nucleotide sequence of the antisense molecules may correspond exactly to a region or portion of <400>1 or <400>2 or may differ by one or more nucleotide substitutions, deletions and/or additions. It is a requirement, however, that the nucleic acid molecule interact with an mRNA molecule to thereby reduce its translation into active protein.

5

Examples of potential antisense molecules for IGFBP-2 and IGFBP-3 are those capable of interacting with sequences selected from the lists in Examples 6 and 7, respectively.

The nucleic acid molecules in the form of an antisense molecule may be linear or covalently  
10 closed circular and single stranded or partially double stranded. A double stranded molecule may form a triplex with target mRNA or a target gene. The molecule may also be protected from, for example, nucleases, by any number of means such as using a nonionic backbone or a phosphorothioate linkage. A convenient nonionic backbone contemplated herein is ethylphosphotriester linkage or a 2'-O-methylribosyl derivative. A particularly useful  
15 modification modifies the DNA backbone by introducing phosphorothioate internucleotide linkages. Alternatively or in addition to the pyrimidine bases are modified by inclusion of a C-5 propyne substitution which modification is proposed to enhance duplex stability [23]. The present invention extends to any chemical modification to the bases and/or RNA or DNA backbone. Reference to a "chemical analogue" of a nucleic acid molecule includes reference  
20 to a modified base, nucleotide, nucleoside or phosphate backbone.

Examples of suitable oligonucleotide analogues are conveniently described in Ts'O *et al* [7]. Further suitable examples of oligonucleotide analogues and chemical modifications are described in references 25 to 31.

25

Alternatively, the antisense molecules of the present invention may target the IGF-I gene itself or its receptor or a multivalent antisense molecule may be constructed or separate molecules administered which target at least two or an IGFBP, IGF-I and/or IGF-I-receptor. Examples of suitable antisense molecules capable of targetting the IGF-I receptor are those capable of

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interacting with sequences selected from the list in Example 8. One particularly useful antisense molecule is 5'- ATCTCTCCGCTTCCTTTC -3' (<400>10).

Other particularly useful antisense molecules are:

- 5 #27 UCCGGAGCCAGACUU  
#64 CACAGUUGCUGCAAG  
#78 UCUCCGCUUCCUUUC  
#28 AGCCCCCACAGCGAG  
#32 GCCUUGGAGAUGAGC  
10 #40 UAACAGAGGUCAGCA  
#42 GGAUCAGGGACCAGU  
#46 CGGCAAGCUACACAG  
#50 GGCAGGCAGGCACAC

- 15 Particularly useful molecules are selected from #27, #64 and #78. In a preferred embodiment these molecules comprise a C-5 propynyl dU, dC phosphorothioate modification.

A particularly preferred embodiment of the present invention contemplates a method of ameliorating the effects of psoriasis or other medical disorder, said method comprising  
20 contacting proliferating skin or skin capable of proliferation or cells associated with said medical disorder with an effective amount of one or more nucleic acid molecules or chemical analogues thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation or ameliorating the medical disorder wherein said one or more molecules comprises a polynucleotide capable of interacting with mRNA directed from an IGF-I gene, an IGF-I  
25 receptor gene or a gene encoding an IGFBP such as IGFBP-2 and/or IGFBP-3.

Preferably, the nucleic acid molecule are antisense molecules. Particularly useful antisense molecules are:

- #27 UCCGGAGCCAGACUU  
30 #64 CACAGUUGCUGCAAG

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#78 UCUCCGCUUCCUUUC  
#28 AGCCCCACAGCGAG  
#32 GCCUUGGAGAUGAGC  
#40 UAACAGAGGUCAGCA  
5 #42 GGAUCAGGGACCAGU  
#46 CGGCAAGCUACACAG  
#50 GGCAGGCAGGCACAC

Even more particularly useful molecules are selected from #27, #64 and #78.

10

In accordance with one aspect of the present invention the nucleic acid molecule is topically applied in aqueous solution or in conjunction with a cream, ointment, oil or other suitable carrier and/or diluent. A single application may be sufficient depending on the severity or exigencies of the condition although more commonly, multiple applications are required ranging from  
15 hourly, multi-hourly, daily, multi-daily, weekly or monthly, or in some other suitable time interval. The treatment might comprise solely the application of the nucleic acid molecule or this may be applied in conjunction with other treatments for the skin proliferation and/or inflammatory disorder being treated or for other associated conditions including microbial infection, bleeding and the formation of a variety of rashes.

20

As an alternative to or in conjunction with antisense therapy, the subject invention extends to the nucleic acid molecule as, or incorporating, a ribozyme including a minizyme to, for example, IGF-I, its receptor or to molecules such as IGFBPs and in particular IGFBP-2 and -3. Ribozymes are synthetic nucleic acid molecules which possess highly specific endoribonuclease  
25 activity. In particular, they comprise a hybridising region which is complementary in nucleotide sequence to at least part of a target RNA. Ribozymes are well described by Haseloff and Gerlach [8] and in International Patent Application No. WO 89/05852. The present invention extends to ribozymes which target mRNA specified by genes encoding IGF-I, its receptor or one or more IGFBPs such as IGFBP-2 and/or IGFBP-3.

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According to this embodiment, there is provided in a particularly preferred aspect a ribozyme comprising a hybridising region and a catalytic region wherein the hybridising region is capable of hybridising to at least part of a target mRNA sequence transcribed from a genomic gene corresponding to (<400>1) or (<400>2) wherein said catalytic domain is capable of cleaving  
5 said target mRNA sequence to reduce or inhibit IGF-I mediated cell proliferation and/or inflammation and/or other medical disorders.

Yet another aspect of the present invention contemplates co-suppression to reduce expression or to inhibit translation of an endogenous gene encoding, for example, IGF-I, its receptor, or  
10 IGFBPs such as IGFBP-2 and/or -3. In co-suppression, a second copy of an endogenous gene or a substantially similar copy or analogue of an endogenous gene is introduced into a cell following topical administration. As with antisense molecules, nucleic acid molecules defining a ribozyme or nucleic acid molecules useful in co-suppression may first be protected such as by using a nonionic backbone.

15

The efficacy of the nucleic acid molecules of the present invention can be conveniently tested and screened using an *in vitro* system comprising a basal keratinocyte cell line. A particularly useful system comprises the HaCaT cell line described by Boukamp *et al* [9]. In one assay, IGF-I is added to an oligonucleotide treated HaCaT cell line. Alternatively, growth of  
20 oligonucleotide treated HaCaT cells is observed on a feeder layer of irradiated 3T3 fibroblasts. Using such *in vitro* assays, it is observed that antisense oligonucleotides to IGFBP-3, for example, inhibit production of IGFBP-3 by HaCaT cells. Other suitable animal models include the nude mouse/human skin graft model (15; 16) and the "flaky skin" mouse model (17; 18). In the nude mouse model, microdermatome biopsies of psoriasis lesions are taken under  
25 local anaesthetic from volunteers then transplanted to congenital athymic (nude) mice. These transplanted human skin grafts maintain the characteristic hyperproliferating epidermis for 6-8 weeks. They are an established model for testing the efficacy of topically applied therapies for psoriasis. In the "flaky skin" mouse model, the *fsn/fsn* mutation produces mice with skin resembling human psoriasis. This mouse, or another mutant mouse with a similar phenotype  
30 is a further *in vivo* model to test the efficacy of topically applied therapies for psoriasis.



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Another aspect of the present invention contemplates a pharmaceutical composition for topical administration which comprises a nucleic acid molecule capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation such as psoriasis and one or more pharmaceutically acceptable carriers and/or diluents. Preferably, the nucleic acid molecule is an antisense  
5 molecule to IGF-I, the IGF-I receptor or an IGFBP such as IGFBP-2 and/or IGFBP-3 or comprises a ribozyme to one or more of these targets or is a molecule suitable for co-suppression of one or more of these targets. The composition may comprise a single species of a nucleic acid molecule capable of targeting one of IGF-I, its receptor or an IGFBP, such as IGFBP-2 or IGFBP-3 or may be a multi-valent molecule capable of targeting two or more of  
10 IGF-I, its receptor or an IGFBP, such as IGFBP-2 and/or IGFBP-3.

The nucleic acid molecules may be administered in dispersions prepared in creams, ointments, oil or other suitable carrier and/or diluent such as glycerol, liquid polyethylene glycols and/or mixtures thereof. Under ordinary conditions of storage and use, these preparations may contain  
15 a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for topical use include sterile aqueous solutions (where water soluble) or dispersions and powders for the extemporaneous preparation of topical solutions or dispersions. In all cases, the form is preferably sterile although this is not an absolute  
20 requirement and is stable under the conditions of manufacture and storage. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of  
25 dispersion and by the use of surfactants. The prevention of the action of microorganism can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride.

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Topical solutions are prepared by incorporating the nucleic acid molecule compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by where necessary filter sterilization.

- 5 The active agent may alternatively be administered by intravenous, subcutaneous, nasal drip, suppository, implant means amongst other suitable routes of administration including intraperitoneal, intramuscular, absorption through epithelial or mucocutaneous linings for example via nasal, oral, vaginal, rectal or gastrointestinal administration. Reference may conveniently be made to reference 24.

10

As used herein "pharmaceutically acceptable carriers and/or diluents" include any and all solvents, dispersion media, aqueous solutions, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional  
15 media or agent is incompatible with the active ingredient, use thereof in the pharmaceutical compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. Conveniently, the nucleic acid molecules of the present invention are stored in freeze-dried form and are reconstituted prior to use.

- 20 Yet another aspect of the present invention contemplates the use of a nucleic acid molecule in the manufacture of a medicament for the treatment of proliferative and/or inflammatory skin disorders or other medical disorders mediated by a growth factor. The proliferative and/or inflammatory skin disorder is generally psoriasis or other medical disorders as described above and the nucleic acid molecule targets IGF-I, the IGF-I receptor and/or an IGFBP such as IGFBP-  
25 2 and/or IGFBP-3.

Still a further aspect of the present invention contemplates an agent comprising a nucleic acid molecule as hereinbefore defined useful in the treatment of proliferative and/or inflammatory skin disorders, such as psoriasis or other medical disorder..

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- 30 -

The present invention further contemplates the use of the genetic molecules and in particular the antisense molecules to inhibit the anti-apoptotic activity of IGF-I receptor. Such a use is appropriate for the treatment of certain cancers and as adjunct therapy for epidermal hyperplasia such as in combination with UV treatment.

5

The present invention is further described by the following non-limiting Examples.

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**EXAMPLE 1**

The differentiated human keratinocyte cell line, HaCaT [9] was used in the *in vitro* assay. Cells at passage numbers 33 to 36 were maintained as monolayer cultures in 5% v/v CO<sub>2</sub> at 37°C in Keratinocyte-SFM (Gibco) containing EGF and bovine pituitary extract as supplied. Media containing foetal calf serum were avoided because of the high content of IGF-I binding proteins in serum.

Feeder layer plates of lethally irradiated 3T3 fibroblasts were prepared exactly as described by Rheinwald and Green [10].

10

**EXAMPLE 2**

Cells were grown to 4 days post confluence in 2cm<sup>2</sup> wells with daily medium changes of Keratinocyte-SFM, then the medium was changed to DMEM (Cytosystems, Australia), with the following additions: 25mM Hepes, 0.19% w/v, sodium bicarbonate, 0.03% w/v glutamine (Sigma Chemical Co, USA), 50IU/ml penicillin and 50µg/ml streptomycin (Flow Laboratories). After 24 hours, IGF-I or tIGF-I was added to triplicate wells, at the concentrations indicated, in 0.5ml fresh DMEM containing 0.02% v/v bovine serum albumin (Sigma molecular biology grade) and incubated for a further 21 hours. [<sup>3</sup>H]-Thymidine (0.1µCi/well) was then added and the cells incubated for a further 3 hours. The medium was then aspirated and the cells washed once with ice-cold PBS and twice with ice-cold 10% v/v TCA. The TCA-precipitated monolayers were then solubilized with 0.25M NaOH (200µl/well), transferred to scintillation vials and radioactivity determined by liquid scintillation counting (Pharmacia Wallac 1410 liquid scintillation counter).

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**EXAMPLE 3**

HaCaT conditioned medium (250µl) was concentrated by adding 750µl cold ethanol, incubating at -20°C for 2 hours and centrifuging at 16,000g for 20 min at 4°C. The resulting pellet was air dried, resuspended thoroughly in non-reducing Laemmli sample buffer, heated to 90°C for 5 minutes and separated on 12% w/v SDS-PAGE according to the method of Laemmli (1970). Separated proteins were electrophoretically transferred to nitrocellulose membrane (0.45mm, Schleicher and Schuell, Dassel, Germany) in a buffer containing 25mM Tris, 192mM glycine

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and 20% v/v methanol. IGFBPs were then visualised by the procedure of Hossenlopp *et al* [11], using [<sup>125</sup>I]-IGF-I, followed by autoradiography. Autoradiographs were scanned in a BioRad Model GS-670 Imaging Densitometer and band densities were determined using the Molecular Analyst program.

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#### EXAMPLE 4

Phosphorothioate oligodeoxynucleotides were synthesised by Bresatec, Adelaide, South Australia, Australia. The following antisense sequences were used: BP3AS2, 5'- GCG CCC GCT GCA TGA CGC CTG CAA C -3' (<400>4), a 25mer complementary to the start codon region of the human IGFBP-3 mRNA; BP3AS3, 5'- CGG GCG GCT CAC CTG GAG CTG GCG -3' (<400>5), a 24mer complementary to the exon 1/intron 1 splice site; BP3AS4, 5'- AGG CGG CTG ACG GCA CTA -3' (<400>6), an 18mer complementary to a region of the coding sequence lacking RNA secondary structure and oligonucleotide-dimer formation (using the computer software "OLIGO for PC"). Since BP3AS4 was found to be ineffective at inhibiting IGFBP-3 synthesis, it was used as a control. The following additional control oligonucleotide sequences were used: BP3S, 5'- CAG GCG TCA TGC AGC GGG C -3' (<400>7), an 18mer sense control sequence equivalent to the start codon region; BP3AS2NS, 5'- CGG AGA TGC CGC ATG CCA GCG CAG G -3' (<400>8), a 25mer randomised sequence with the same GC content as BP3AS2; BP3AS4NS, 5'- GAC AGC GTC GGA GCG ATC -3' (<400>9), an 18mer randomised sequence with the same GC content as BP3AS4NS. Design of the oligonucleotides was based on the human IGFBP-3 cDNA sequence of Spratt *et al* [12].

Cells were grown to one day post confluence in 2cm<sup>2</sup> wells with daily medium changes of 0.5ml Keratinocyte-SFM, then subjected to daily medium changes of Keratinocyte-SFM for a further 4 days. Daily additions of 0.5ml fresh Keratinocyte-SFM were then continued for a further 7 days, except that at the time of medium addition, 5µl oligonucleotide in PBS was added to give the final concentrations indicated, then the wells were shaken to mix the oligonucleotide. After the final addition, cells were incubated for 24 hours and the medium collected for assay of IGFBPs. Cells were then counted after trypsinisation in a Coulter Industrial D Counter, Coulter Bedfordshire, UK. Cell numbers after oligonucleotide treatment differed by less than 10%.

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### EXAMPLE 5

HaCaT cells secrete mainly IGFBP-3 (>95%), with the only other IGFBP detectable in HaCaT conditioned medium being IGFBP-4 (<5%). The effect on IGFBP-3 and IGFBP-4 synthesis of antisense oligonucleotides at two concentrations, 5 $\mu$ M and 0.5 $\mu$ M, was tested. Two oligonucleotides were used, BP3AS2 and BP3AS3, directed against the start site and the intron 1/exon 1 splice site, respectively of the IGFBP-3 mRNA. As a control, a sense oligonucleotide corresponding to the start site was used. As shown in Figures 4A and 4B, all oligonucleotides at 5 $\mu$ M caused a significant reduction of IGFBP-3 synthesis compared with untreated cells, however, the two antisense oligonucleotides inhibited IGFBP-3 synthesis of approximately 50% compared to the sense control (Figure 4B). The antisense oligonucleotide directed to the start codon appeared to be more effective of the two, the difference being more apparent at the lower concentration of 0.5 $\mu$ M. The cells of IGFBP-4 secreted by the HaCaT cells make photographic reproduction of the bands on Western ligand blots difficult, however densitometry measurements provide adequate relative quantitation. This resulted in the significant observation that IGFBP-4 levels were unaffected by oligonucleotide addition to the cells, suggesting that the observed inhibitory effects on IGFBP-3 are specific.

To further investigate the inhibitory effects of the more effective of the two antisense oligonucleotides, BP3AS2, inhibition by this oligonucleotide at 0.5 $\mu$ M was compared with a number of control oligonucleotides, including one antisense oligonucleotide to IGFBP-3 that had proved to be ineffective at 0.5 $\mu$ M. As shown in Figures 5A and 5B, BP3AS2 was again inhibitory, resulting in levels of IGFBP-3 of approximately 50% of the most non-specifically inhibitory control oligonucleotide, the randomised equivalent of BP3AS2. The other control oligonucleotides caused no reduction in IGFBP-3 levels at 0.5 $\mu$ M, compared to untreated cells. Of possible significance is the fact that this control oligonucleotide, BP3AS2NS, like BP3AS2 itself, has the highest potential  $T_m$  of the three control oligonucleotides used in this experiment, enhancing the probability of non-specific base pairing with non-target mRNAs. However, the lack of inhibition of IGFBP-4 secretion by BP3AS2 suggests that this oligonucleotide is selective even compared with the most closely related protein likely to be present in this cell

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**EXAMPLE 6**

Antisense oligonucleotides to IGFBP2 may be selected from molecules capable of interacting with one or more of the following sense oligonucleotides:

	ATTCGGGGCGAGGGA	CGCAGGGCCGTGCAC	CCGCGCCGCGCTGCC
5	TTCGGGGCGAGGGAG	GCAGGGCCGTGCACC	CGCGCCGCGCTGCCG
	TCGGGGCGAGGGAGG	CAGGGCCGTGCACCT	GCGCCGCGCTGCCGA
	CGGGGCGAGGGAGGA	AGGGCCGTGCACCTG	CGCCGCGCTGCCGAC
	GGGGGCGAGGGAGGAG	GGGCCGTGCACCTGC	GCCGCGCTGCCGACC
	GGGCGAGGGAGGAGG	GGCCGTGCACCTGCC	CCGCGCTGCCGACCG
10	GGCGAGGGAGGAGGA	GCCGTGCACCTGCCC	CGCGCTGCCGACCGC
	GCGAGGGAGGAGGAA	CCGTGCACCTGCCCG	GCGCTGCCGACCGCC
	CGAGGGAGGAGGAAG	CGTGCACCTGCCCGC	CGCTGCCGACCGCCA
	GAGGGAGGAGGAAGA	GTGCACCTGCCCGCC	GCTGCCGACCGCCAG
	AGGGAGGAGGAAGAA	TGCACCTGCCCGCCC	CTGCCGACCGCCAGC
15	GGGAGGAGGAAGAAG	GCACCTGCCCGCCCG	TGCCGACCGCCAGCA
	GGAGGAGGAAGAAGC	CACCTGCCCGCCCGC	GCCGACCGCCAGCAT
	GAGGAGGAAGAAGCG	ACCTGCCCGCCCGCC	CCGACCGCCAGCATG
	AGGAGGAAGAAGCGG	CCTGCCCGCCCGCCC	CGACCGCCAGCATGC
	GGAGGAAGAAGCGGA	CTGCCCGCCCGCCCG	GACCGCCAGCATGCT
20	GAGGAAGAAGCGGAG	TGCCCGCCCGCCCGC	ACCGCCAGCATGCTG
	AGGAAGAAGCGGAGG	GCCCGCCCGCCCGCT	CCGCCAGCATGCTGC
	GGAAGAAGCGGAGGA	CCCGCCCGCCCGCTC	CGCCAGCATGCTGCC
	GAAGAAGCGGAGGAG	CCGCCCGCCCGCTCG	GCCAGCATGCTGCCG
	AAGAAGCGGAGGAGG	CGCCCGCCCGCTCGC	CCAGCATGCTGCCGA
25	AGAAGCGGAGGAGGC	GCCCGCCCGCTCGCT	CAGCATGCTGCCGAG
	GAAGCGGAGGAGGCG	CCCGCCCGCTCGCTC	AGCATGCTGCCGAGA
	AAGCGGAGGAGGCGG	CCGCCCGCTCGCTCG	GCATGCTGCCGAGAG
	AGCGGAGGAGGCGGC	CGCCCGCTCGCTCGC	CATGCTGCCGAGAGT
	GCGGAGGAGGCGGCT	GCCCGCTCGCTCGCT	ATGCTGCCGAGAGTG
30	CGGAGGAGGCGGCTC	CCCGCTCGCTCGCTC	TGCTGCCGAGAGTGG
	GGAGGAGGCGGCTCC	CCGCTCGCTCGCTCG	GCTGCCGAGAGTGGG
	GAGGAGGCGGCTCCC	CGCTCGCTCGCTCGC	CTGCCGAGAGTGGGC
	AGGAGGCGGCTCCCG	GCTCGCTCGCTCGCC	TGCCGAGAGTGGGCT
	GGAGGCGGCTCCCGC	CTCGCTCGCTCGCCC	GCCGAGAGTGGGCTG
35	GAGGCGGCTCCCGCT	TCGCTCGCTCGCCCG	CCGAGAGTGGGCTGC
	AGGCGGCTCCCGCTC	CGCTCGCTCGCCCGC	CGAGAGTGGGCTGCC
	GGCGGCTCCCGCTCG	GCTCGCTCGCCCGCC	GAGAGTGGGCTGCCC
	GCGGCTCCCGCTCGC	CTCGCTCGCCCGCCG	AGAGTGGGCTGCCCC
	CGGCTCCCGCTCGCA	TCGCTCGCCCGCCGC	GAGTGGGCTGCCCCG
40	GGCTCCCGCTCGCAG	CGCTCGCCCGCCGCG	AGTGGGCTGCCCCGC
	GCTCCCGCTCGCAGG	GCTCGCCCGCCGCGC	GTGGGCTGCCCCGCG
	CTCCCGCTCGCAGGG	CTCGCCCGCCGCGCC	TGGGCTGCCCCGCGC
	TCCCGCTCGCAGGGC	TCGCCCGCCGCGCCG	GGGCTGCCCCGCGCT
	CCCGCTCGCAGGGCC	CGCCCGCCGCGCCGC	GGCTGCCCCGCGCTG
45	CCGCTCGCAGGGCCG	GCCCGCCGCGCCGCG	GCTGCCCCGCGCTGC
	CGCTCGCAGGGCCGT	CCCGCCGCGCCGCGC	CTGCCCCGCGCTGCC
	GCTCGCAGGGCCGTG	CCGCCGCGCCGCGCT	TGCCCGCGCTGCCG
	CTCGCAGGGCCGTGC	CGCCCGCGCCGCGTG	GCCCCGCGCTGCCG
	TCGCAGGGCCGTGCA	GCCGCGCCGCGCTGC	CCCCGCGCTGCCGCT

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CCCCGCGCTGCCGCTG	CTGCTGCTACTGGGC	CTGTTCCGCTGCCCCG
CCGCGCTGCCGCTGC	TGCTGCTACTGGGCG	TGTTCCGCTGCCCCGC
CGCGCTGCCGCTGCC	GCTGCTACTGGGCGC	GTTCCGCTGCCCCGCC
GCGCTGCCGCTGCCG	CTGCTACTGGGCGCG	FTCCGCTGCCCCGCCC
5 CGCTGCCGCTGCCGC	TGCTACTGGGCGCGA	TCCGCTGCCCCGCCCT
GCTGCCGCTGCCGCC	GCTACTGGGCGCGAG	CCGCTGCCCCGCCCTG
CTGCCGCTGCCGCCG	CTACTGGGCGCGAGT	CGCTGCCCCGCCCTGC
TGCCGCTGCCGCCGC	TACTGGGCGCGAGTG	GCTGCCCCGCCCTGCA
GCCGCTGCCGCCGCC	ACTGGGCGCGAGTGG	CTGCCCCGCCCTGCAC
10 CCGCTGCCGCCGCCG	CTGGGCGCGAGTGGC	TGCCCCGCCCTGCACA
CGCTGCCGCCGCCGC	TGGGCGCGAGTGGCG	GCCCCGCCCTGCACAC
GCTGCCGCCGCCGCC	GGGCGCGAGTGGCGG	CCCGCCCTGCACACC
CTGCCGCCGCCGCCG	GGCGCGAGTGGCGGC	CCGCCCTGCACACCC
TGCCGCCGCCGCCGC	GCGCGAGTGGCGGCG	CGCCCTGCACACCCG
15 GCCGCCGCCGCCGCT	CGCGAGTGGCGGCGG	GCCCTGCACACCCGA
CCGCCGCCGCCGCTG	GCGAGTGGCGGCGGC	CCCTGCACACCCGAG
CGCCGCCGCCGCTGC	CGAGTGGCGGCGGCG	CCTGCACACCCGAGC
GCCGCCGCCGCTGCT	GAGTGGCGGCGGCGG	CTGCACACCCGAGCG
CCGCCGCCGCTGCTG	AGTGGCGGCGGCGGC	TGCACACCCGAGCGC
20 CGCCGCCGCTGCTGC	GTGGCGGCGGCGGCG	GCACACCCGAGCGCC
GCCGCCGCTGCTGCC	TGGCGGCGGCGGCGG	CACACCCGAGCGCCT
CCGCCGCTGCTGCCG	GGCGGCGGCGGCGGG	ACACCCGAGCGCCTG
CGCCGCTGCTGCCGC	GCGGCGGCGGCGGGG	CACCCGAGCGCCTGG
GCCGCTGCTGCCGCT	CGGCGGCGGCGGGGC	ACCCGAGCGCCTGGC
25 CCGCTGCTGCCGCTG	GGCGGCGGCGGGGCG	CCCGAGCGCCTGGCC
CGCTGCTGCCGCTGC	GCGGCGGCGGGGCGC	CCGAGCGCCTGGCCG
GCTGCTGCCGCTGCT	CGGCGGCGGGGCGCG	CGAGCGCCTGGCCGC
CTGCTGCCGCTGCTG	GGCGGCGGGGCGCGC	GAGCGCCTGGCCGCC
TGCTGCCGCTGCTGC	GCGGCGGGGCGCGCG	AGCGCCTGGCCGCCT
30 GCTGCCGCTGCTGCC	CGGCGGGGCGCGCGC	GCGCCTGGCCGCCTG
CTGCCGCTGCTGCCG	GGCGGGGCGCGCGCG	CGCCTGGCCGCCTGC
TGCCGCTGCTGCCGC	GCGGGGCGCGCGCGG	GCCTGGCCGCCTGCG
GCCGCTGCTGCCGCT	CGGGGCGCGCGCGGA	CCTGGCCGCCTGCGG
CCGCTGCTGCCGCTG	GGGGCGCGCGCGGAG	CTGGCCGCCTGCGGG
35 CGCTGCTGCCGCTGC	GGGCGCGCGCGGAGG	TGGCCGCCTGCGGGC
GCTGCTGCCGCTGCT	GGCGCGCGCGGAGGT	GGCCGCCTGCGGGCC
CTGCTGCCGCTGCTG	GCGCGCGCGGAGGTG	GCCGCCTGCGGGCCC
TGCTGCCGCTGCTGC	CGCGCGCGGAGGTGC	CCGCCTGCGGGCCCC
GCTGCCGCTGCTGCT	GCGCGCGGAGGTGCT	CGCCTGCGGGCCCCC
40 CTGCCGCTGCTGCTG	CGCGCGGAGGTGCTG	GCCTGCGGGCCCCCG
TGCCGCTGCTGCTGC	GCGCGGAGGTGCTGT	CCTGCGGGCCCCCGC
GCCGCTGCTGCTGCT	CGCGGAGGTGCTGTT	CTGCGGGCCCCCGCC
CCGCTGCTGCTGCTG	GCGGAGGTGCTGTTCC	TGCGGGCCCCCGCCG
CGCTGCTGCTGCTGC	GGAGGTGCTGTTCCG	GCGGGCCCCCGCCGG
45 GCTGCTGCTGCTGCT	GAGGTGCTGTTCCGC	CGGGCCCCCGCCGGT
CTGCTGCTGCTGCTA	AGGTGCTGTTCCGCT	GGGGCCCCCGCCGGT
TGCTGCTGCTGCTAC	GGTGTGTTCCGCTG	GGCCCCCGCCGGTTG
GCTGCTGCTGCTACT	GTGCTGTTCCGCTGC	GCCCCCGCCGGTTGC
CTGCTGCTGCTACTG	TGCTGTTCCGCTGCC	CCCCCGCCGGTTGCG
50 TGCTGCTGCTACTGG	GCTGTTCCGCTGCCC	CCCCCGCGTTGCGCC
GCTGCTGCTACTGGG		



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	CCGCCCGGTTGCGCCG	ATGCCATGCGCGGAG	TGCGCCCGGCTGGAG
	CGCCGGTTGCGCCGC	TGCCATGCGCGGAGC	GCGCCCGGCTGGAGG
	GCCGGTTGCGCCGCC	GCCATGCGCGGAGCT	CGCCCGGCTGGAGGG
	CCGGTTGCGCCGCCC	CCATGCGCGGAGCTC	GCCCGGCTGGAGGGC
5	CGGTTGCGCCGCCCC	CATGCGCGGAGCTCG	CCCGGCTGGAGGGCG
	GGTTGCGCCGCCCCG	ATGCGCGGAGCTCGT	CCGGCTGGAGGGCGA
	GTTGCGCCGCCCCGC	TGCGCGGAGCTCGTC	CGGCTGGAGGGCGAG
	TTGCGCCGCCCCGCG	GCGCGGAGCTCGTCC	GGCTGGAGGGCGAGG
	TGCGCCGCCCCGCCG	CGCGGAGCTCGTCCG	GCTGGAGGGCGAGGC
10	GCGCCGCCCCGCCGCG	GCGGAGCTCGTCCGG	CTGGAGGGCGAGGCG
	CGCCGCCCCGCCGCGG	CGGAGCTCGTCCGGG	TGGAGGGCGAGGCGT
	GCCGCCCCGCCGCGGT	GGAGCTCGTCCGGGA	GGAGGGCGAGGCGTG
	CCGCCCCGCCGCGGTG	GAGCTCGTCCGGGAG	GAGGGCGAGGCGTGC
	CGCCCCGCCGCGGTGG	AGCTCGTCCGGGAGC	AGGGCGAGGCGTGCG
15	GCCCCGCCGCGGTGGC	GCTCGTCCGGGAGCC	GGGCGAGGCGTGCGG
	CCCCGCCGCGGTGGCC	CTCGTCCGGGAGCCG	GGCGAGGCGTGCGGC
	CCGCCGCGGTGGCCG	TCGTCCGGGAGCCGG	GCGAGGCGTGCGGCG
	CGCCGCGGTGGCCGC	CGTCCGGGAGCCGGG	CGAGGCGTGCGGCGT
	GCCGCGGTGGCCGCA	GTCCGGGAGCCGGGC	GAGGCGTGCGGCGTC
20	CCGCGGTGGCCGCAG	TCCGGGAGCCGGGCT	AGGCGTGCGGCGTCT
	CGCGGTGGCCGCAGT	CCGGGAGCCGGGCTG	GGCGTGCGGCGTCTA
	GCGGTGGCCGCAGTG	CGGGAGCCGGGCTGC	GCGTGCGGCGTCTAC
	CGGTGGCCGCAGTGG	GGGAGCCGGGCTGCG	CGTGCGGCGTCTACA
	GGTGGCCGCAGTGGC	GGAGCCGGGCTGCGG	GTGCGGCGTCTACAC
25	GTGGCCGCAGTGGCC	GAGCCGGGCTGCGGC	TGCGGCGTCTACACC
	TGGCCGCAGTGGCCG	AGCCGGGCTGCGGCT	GCGGCGTCTACACCC
	GGCCGCAGTGGCCGG	GCCGGGCTGCGGCTG	CGGCGTCTACACCCC
	GCCGCAGTGGCCGGA	CCGGGCTGCGGCTGC	GGCGTCTACACCCCC
	CCGCAGTGGCCGGAG	CGGGCTGCGGCTGCT	GCGTCTACACCCCCG
30	CGCAGTGGCCGGAGG	GGGCTGCGGCTGCTG	CGTCTACACCCCCGCG
	GCAGTGGCCGGAGGC	GGCTGCGGCTGCTGC	GTCTACACCCCCGCGC
	CAGTGGCCGGAGGCG	GCTGCGGCTGCTGCT	TCTACACCCCCGCGCT
	AGTGGCCGGAGGCGC	CTGCGGCTGCTGCTC	CTACACCCCCGCGCTG
	GTGGCCGGAGGCGCC	TGCGGCTGCTGCTCG	TACACCCCCGCGCTGC
35	TGGCCGGAGGCGCCC	GCGGCTGCTGCTCGG	ACACCCCCGCGCTGCG
	GGCCGGAGGCGCCCC	CGGCTGCTGCTCGGT	CACCCCGCGCTGCGG
	GCCGGAGGCGCCCCG	GGCTGCTGCTCGGTG	ACCCCGCGCTGCGGC
	CCGGAGGCGCCCCGA	GCTGCTGCTCGGTGT	CCCCGCGCTGCGGCC
	CGGAGGCGCCCCCAT	CTGCTGCTCGGTGTG	CCCGCGCTGCGGCCA
40	GGAGGCGCCCCGCATG	TGCTGCTCGGTGTGC	CCGCGCTGCGGCCAG
	GAGGCGCCCCGCATGC	GCTGCTCGGTGTGCG	CGCGCTGCGGCCAGG
	AGGCGCCCCGCATGCC	CTGCTCGGTGTGCGC	GCGCTGCGGCCAGGG
	GGCGCCCCGCATGCCA	TGCTCGGTGTGCGCC	CGCTGCGGCCAGGGG
	GCGCCCCGCATGCCAT	GCTCGGTGTGCGCCC	GCTGCGGCCAGGGGC
45	CGCCCCGCATGCCATG	CTCGGTGTGCGCCCG	CTGCGGCCAGGGGCT
	GCCCGCATGCCATGC	TCGGTGTGCGCCCGG	TGCGGCCAGGGGCTG
	CCCGCATGCCATGCG	CGGTGTGCGCCCGGC	GCGGCCAGGGGCTGCG
	CCGCATGCCATGCGC	GGTGTGCGCCCGGCT	GGCCAGGGGCTGCGC
	CGCATGCCATGCGCG	GTGTGCGCCCGGCTG	GCCAGGGGCTGCGCT
50	GCATGCCATGCGCGG	TGTGCGCCCGGCTGG	CCAGGGGCTGCGCTG
	CATGCCATGCGCGGA	GTGCGCCCGGCTGGA	

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CAGGGGCTGCGCTGC	CTGGTCATGGGCGAG	GCCAGCCCGGAGCAG
AGGGGCTGCGCTGCT	TGGTCATGGGCGAGG	CCAGCCCGGAGCAGG
GGGGCTGCGCTGCTA	GGTCATGGGCGAGGG	CAGCCCGGAGCAGGT
GGGCTGCGCTGCTAT	GTCATGGGCGAGGGC	AGCCCGGAGCAGGTT
5 GGCTGCGCTGCTATC	TCATGGGCGAGGGCA	GCCCGGAGCAGGTTG
GCTGCGCTGCTATCC	CATGGGCGAGGGCAC	CCCGGAGCAGGTTGC
CTGCGCTGCTATCCC	ATGGGCGAGGGCACT	CCGGAGCAGGTTGCA
TGCGCTGCTATCCCC	TGGGCGAGGGCACTT	CGGAGCAGGTTGCAG
GCGCTGCTATCCCCA	GGGCGAGGGCACTTG	GGAGCAGGTTGCAGA
10 CGCTGCTATCCCCAC	GGCGAGGGCACTTGT	GAGCAGGTTGCAGAC
GCTGCTATCCCCACC	GCGAGGGCACTTGTG	AGCAGGTTGCAGACA
CTGCTATCCCCACCC	CGAGGGCACTTGTGA	GCAGGTTGCAGACAA
TGCTATCCCCACCCG	GAGGGCACTTGTGAG	CAGGTTGCAGACAAT
GCTATCCCCACCCGG	AGGGCACTTGTGAGA	AGGTTGCAGACAATG
15 CTATCCCCACCCGGG	GGGCACTTGTGAGAA	GGTTGCAGACAATGG
TATCCCCACCCGGGC	GGCACTTGTGAGAAG	GTTGCAGACAATGGC
ATCCCCACCCGGGCT	GCACTTGTGAGAAGC	TTGCAGACAATGGCG
TCCCCACCCGGGCTC	CACTTGTGAGAAGCG	TGCAGACAATGGCGA
CCCCACCCGGGCTCC	ACTTGTGAGAAGCGC	GCAGACAATGGCGAT
20 CCCACCCGGGCTCCG	CTTGTGAGAAGCGCC	CAGACAATGGCGATG
CCACCCGGGCTCCGA	TTGTGAGAAGCGCCG	AGACAATGGCGATGA
CACCCGGGCTCCGAG	TGTGAGAAGCGCCGG	GACAATGGCGATGAC
ACCCGGGCTCCGAGC	GTGAGAAGCGCCGGG	ACAATGGCGATGACC
CCCGGGCTCCGAGCT	TGAGAAGCGCCGGGA	CAATGGCGATGACCA
25 CCGGGCTCCGAGCTG	GAGAAGCGCCGGGAC	AATGGCGATGACCAC
CGGGCTCCGAGCTGC	AGAAGCGCCGGGACG	ATGGCGATGACCACT
GGGCTCCGAGCTGCC	GAAGCGCCGGGACGC	TGGCGATGACCACTC
GGCTCCGAGCTGCCC	AAGCGCCGGGACGCC	GGCGATGACCACTCA
GCTCCGAGCTGCCCC	AGCGCCGGGACGCCG	GCGATGACCACTCAG
30 CTCCGAGCTGCCCCCT	GCGCCGGGACGCCGA	CGATGACCACTCAGA
TCCGAGCTGCCCCCTG	CGCCGGGACGCCGAG	GATGACCACTCAGAA
CCGAGCTGCCCCCTGC	GCCGGGACGCCGAGT	ATGACCACTCAGAAG
CGAGCTGCCCCCTGCA	CCGGGACGCCGAGTA	TGACCACTCAGAAGG
GAGCTGCCCCCTGCAG	CGGGACGCCGAGTAT	GACCACTCAGAAGGA
35 AGCTGCCCCCTGCAGG	GGGACGCCGAGTATG	ACCACTCAGAAGGAG
GCTGCCCCCTGCAGGC	GGACGCCGAGTATGG	CCACTCAGAAGGAGG
CTGCCCCCTGCAGGCG	GACGCCGAGTATGGC	CACTCAGAAGGAGGC
TGCCCCCTGCAGGCGC	ACGCCGAGTATGGCG	ACTCAGAAGGAGGCC
GCCCCCTGCAGGCGCT	CGCCGAGTATGGCGC	CTCAGAAGGAGGCCT
40 CCCCTGCAGGCGCTG	GCCGAGTATGGCGCC	TCAGAAGGAGGCCTG
CCCTGCAGGCGCTGG	CCGAGTATGGCGCCA	CAGAAGGAGGCCTGG
CCTGCAGGCGCTGGT	CGAGTATGGCGCCAG	AGAAGGAGGCCTGGT
CTGCAGGCGCTGGTC	GAGTATGGCGCCAGC	GAAGGAGGCCTGGTG
TGCAGGCGCTGGTCA	AGTATGGCGCCAGCC	AAGGAGGCCTGGTGG
45 GCAGGCGCTGGTCAT	GTATGGCGCCAGCCC	AGGAGGCCTGGTGGG
CAGGCGCTGGTCATG	TATGGCGCCAGCCCG	GGAGGCCTGGTGGAG
AGGCGCTGGTCATGG	ATGGCGCCAGCCCGG	GAGGCCTGGTGGAGA
GGCGCTGGTCATGGG	TGGCGCCAGCCCGGA	AGGCCTGGTGGAGAA
GCGCTGGTCATGGGC	GGCGCCAGCCCGGAG	GGCCTGGTGGAGAAC
50 CGCTGGTCATGGGCG	GCGCCAGCCCGGAGC	GCCTGGTGGAGAAC
GCTGGTCATGGGCGA	CGCCAGCCCGGAGCA	CCTGGTGGAGAACCA

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	CTGGTGGAGAACCAC	AGTGCTGGCCGGAAG	CGGGAGAAGGTCACT
	TGGTGGAGAACCACG	GTGCTGGCCGGAAGC	GGGAGAAGGTCACTG
	GGTGGAGAACCACGT	TGCTGGCCGGAAGCC	GGAGAAGGTCACTGA
	GTGGAGAACCACGTG	GCTGGCCGGAAGCCC	GAGAAGGTCACTGAG
5	TGGAGAACCACGTGG	CTGGCCGGAAGCCCC	AGAAGGTCACTGAGC
	GGAGAACCACGTGGA	TGGCCGGAAGCCCCT	GAAGGTCACTGAGCA
	GAGAACCACGTGGAC	GGCCGGAAGCCCCTC	AAGGTCACTGAGCAG
	AGAACCACGTGGACA	GCCGGAAGCCCCTCA	AGGTCACTGAGCAGC
	GAACCACGTGGACAG	CCGGAAGCCCCTCAA	GGTCACTGAGCAGCA
10	AACCACGTGGACAGC	CGGAAGCCCCTCAAG	GTCACTGAGCAGCAC
	ACCACGTGGACAGCA	GGAAGCCCCTCAAGT	TCACTGAGCAGCACC
	CCACGTGGACAGCAC	GAAGCCCCTCAAGTC	CACTGAGCAGCACCG
	CACGTGGACAGCACC	AAGCCCCTCAAGTCG	ACTGAGCAGCACCGG
	ACGTGGACAGCACCA	AGCCCCTCAAGTCGG	CTGAGCAGCACCGGC
15	CGTGGACAGCACCAT	GCCCCTCAAGTCGGG	TGAGCAGCACCGGCA
	GTGGACAGCACCATG	CCCCTCAAGTCGGGT	GAGCAGCACCGGCAG
	TGGACAGCACCATGA	CCCTCAAGTCGGGTA	AGCAGCACCGGCAGA
	GGACAGCACCATGAA	CCTCAAGTCGGGTAT	GCAGCACCGGCAGAT
	GACAGCACCATGAAC	CTCAAGTCGGGTATG	CAGCACCGGCAGATG
20	ACAGCACCATGAACA	TCAAGTCGGGTATGA	AGCACCGGCAGATGG
	CAGCACCATGAACAT	CAAGTCGGGTATGAA	GCACCGGCAGATGGG
	AGCACCATGAACATG	AAGTCGGGTATGAAG	CACCGGCAGATGGGC
	GCACCATGAACATGT	AGTCGGGTATGAAGG	ACCGGCAGATGGGCA
	CACCATGAACATGTT	GTCTGGGTATGAAGGA	CCGGCAGATGGGCAA
25	ACCATGAACATGTTG	TCGGGTATGAAGGAG	CGGCAGATGGGCAAG
	CCATGAACATGTTGG	CGGGTATGAAGGAGC	GGCAGATGGGCAAGG
	CATGAACATGTTGGG	GGGTATGAAGGAGCT	GCAGATGGGCAAGGG
	ATGAACATGTTGGGC	GGTATGAAGGAGCTG	CAGATGGGCAAGGGT
	TGAACATGTTGGGCG	GTATGAAGGAGCTGG	AGATGGGCAAGGGTG
30	GAACATGTTGGGCGG	TATGAAGGAGCTGGC	GATGGGCAAGGGTGG
	AACATGTTGGGCGGG	ATGAAGGAGCTGGCC	ATGGGCAAGGGTGGC
	ACATGTTGGGCGGGG	TGAAGGAGCTGGCCG	TGGGCAAGGGTGGCA
	CATGTTGGGCGGGGG	GAAGGAGCTGGCCGT	GGGCAAGGGTGGCAA
	ATGTTGGGCGGGGGA	AAGGAGCTGGCCGTG	GGCAAGGGTGGCAAG
35	TGTTGGGCGGGGGAG	AGGAGCTGGCCGTGT	GCAAGGGTGGCAAGC
	GTTGGGCGGGGGAGG	GGAGCTGGCCGTGTT	CAAGGGTGGCAAGCA
	TTGGGCGGGGGAGGC	GAGCTGGCCGTGTTC	AAGGGTGGCAAGCAT
	TGGGCGGGGGAGGCA	AGCTGGCCGTGTTCC	AGGGTGGCAAGCATC
	GGGCGGGGGAGGCAG	GCTGGCCGTGTTCCG	GGGTGGCAAGCATCA
40	GGCGGGGGAGGCAGT	CTGGCCGTGTTCCGG	GGTGGCAAGCATCAC
	GCGGGGGAGGCAGTG	TGGCCGTGTTCCGGG	GTGGCAAGCATCAC
	CGGGGGAGGCAGTGC	GGCCGTGTTCCGGGA	TGGCAAGCATCACCT
	GGGGGAGGCAGTGCT	GCCGTGTTCCGGGAG	GGCAAGCATCACCTT
	GGGGAGGCAGTGCTG	CCGTGTTCCGGGAGA	GCAAGCATCACCTTG
45	GGGAGGCAGTGCTGG	CGTGTTCGGGAGAA	CAAGCATCACCTTGG
	GGAGGCAGTGCTGGC	GTGTTCGGGAGAAAG	AAGCATCACCTTGGC
	GAGGCAGTGCTGGCC	TGTTCGGGAGAAAGG	AGCATCACCTTGGCC
	AGGCAGTGCTGGCCG	GTTCCGGGAGAAAGT	GCATCACCTTGGCCT
	GGCAGTGCTGGCCGG	TTCCGGGAGAAAGTC	CATCACCTTGGCCTG
50	GCAGTGCTGGCCGGA	TCCGGGAGAAAGTCA	ATCACCTTGGCCTGG
	CAGTGCTGGCCGGA	CCGGGAGAAAGTCAC	TCACCTTGGCCTGGA

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	CACCTTGGCCTGGAG	CCCTGCCAACAGGAA	CTTCCGGATGAGCGG
	ACCTTGGCCTGGAGG	CCTGCCAACAGGAAC	TTCCGGATGAGCGGG
	CCTTGGCCTGGAGGA	CTGCCAACAGGAACT	TCCGGATGAGCGGGG
	CTTGGCCTGGAGGAG	TGCCAACAGGAACTG	CCGGATGAGCGGGGC
5	TTGGCCTGGAGGAGC	GCCAACAGGAACTGG	CGGATGAGCGGGGCC
	TGGCCTGGAGGAGCC	CCAACAGGAACTGGA	GGATGAGCGGGGCC
	GGCCTGGAGGAGCCC	CAACAGGAACTGGAC	GATGAGCGGGGCCCT
	GCCTGGAGGAGCCCA	AACAGGAACTGGACC	ATGAGCGGGGCCCTC
	CCTGGAGGAGCCCAA	ACAGGAACTGGACCA	TGAGCGGGGCCCTCT
10	CTGGAGGAGCCCAAG	CAGGAACTGGACCAG	GAGCGGGGCCCTCTG
	TGGAGGAGCCCAAGA	AGGAACTGGACCAGG	AGCGGGGCCCTCTGG
	GGAGGAGCCCAAGAA	GGAACCTGGACCAGGT	GCGGGGCCCTCTGGA
	GAGGAGCCCAAGAAG	GAACCTGGACCAGGTC	CGGGGCCCTCTGGAG
	AGGAGCCCAAGAAGC	AACTGGACCAGGTCC	GGGGGCCCTCTGGAGC
15	GGAGCCCAAGAAGCT	ACTGGACCAGGTCTCT	GGGCCCTCTGGAGCA
	GAGCCCAAGAAGCTG	CTGGACCAGGTCTCTG	GGCCCTCTGGAGCAC
	AGCCCAAGAAGCTGC	TGGACCAGGTCTCTGG	GCCCTCTGGAGCACCT
	GCCCAAGAAGCTGCG	GGACCAGGTCTCTGGA	CCCTCTGGAGCACCT
	CCCAAGAAGCTGCGA	GACCAGGTCTCTGGAG	CCTCTGGAGCACCTC
20	CCAAGAAGCTGCGAC	ACCAGGTCTCTGGAGC	CTCTGGAGCACCTCT
	CAAGAAGCTGCGACC	CCAGGTCTCTGGAGCG	TCTGGAGCACCTCTA
	AAGAAGCTGCGACCA	CAGGTCTCTGGAGCGG	CTGGAGCACCTCTAC
	AGAAGCTGCGACCAC	AGGTCTCTGGAGCGGA	TGGAGCACCTCTACT
	GAAGCTGCGACCACC	GGTCTCTGGAGCGGAT	GGAGCACCTCTACTC
25	AAGCTGCGACCACCC	GTCTCTGGAGCGGATC	GAGCACCTCTACTCC
	AGCTGCGACCACCCC	TCCTGGAGCGGATCT	AGCACCTCTACTCCC
	GCTGCGACCACCCCC	CCTGGAGCGGATCTC	GCACCTCTACTCCCT
	CTGCGACCACCCCCCT	CTGGAGCGGATCTCC	CACCTCTACTCCCTG
	TGCGACCACCCCCCTG	TGGAGCGGATCTCCA	ACCTCTACTCCCTGC
30	GCGACCACCCCCCTGC	GGAGCGGATCTCCAC	CCTCTACTCCCTGCA
	CGACCACCCCCCTGCC	GAGCGGATCTCCACC	CTCTACTCCCTGCAC
	GACCACCCCCCTGCCA	AGCGGATCTCCACCA	TCTACTCCCTGCACA
	ACCACCCCCCTGCCAG	GCGGATCTCCACCAT	CTACTCCCTGCACAT
	CCACCCCCCTGCCAGG	CGGATCTCCACCATG	TACTCCCTGCACATC
35	CACCCCCCTGCCAGGA	GGATCTCCACCATGC	ACTCCCTGCACATCC
	ACCCCCCTGCCAGGAC	GATCTCCACCATGCG	CTCCCTGCACATCCC
	CCCCCTGCCAGGACT	ATCTCCACCATGCGC	TCCCTGCACATCCCC
	CCCCTGCCAGGACTC	TCTCCACCATGCGCC	CCCTGCACATCCCCA
	CCCTGCCAGGACTCC	CTCCACCATGCGCCT	CCTGCACATCCCCAA
40	CCTGCCAGGACTCCC	TCCACCATGCGCCTT	CTGCACATCCCCAAG
	CTGCCAGGACTCCCT	CCACCATGCGCCTTC	TGCACATCCCCAAGT
	TGCCAGGACTCCCTG	CACCATGCGCCTTCC	GCACATCCCCAAGTG
	GCCAGGACTCCCTGC	ACCATGCGCCTTCCG	CACATCCCCAAGTGT
	CCAGGACTCCCTGCC	CCATGCGCCTTCCGG	ACATCCCCAAGTGTG
45	CAGGACTCCCTGCCA	CATGCGCCTTCCGGA	CATCCCCAAGTGTGA
	AGGACTCCCTGCCAA	ATGCGCCTTCCGGAT	ATCCCCAAGTGTGAC
	GGACTCCCTGCCAAC	TGCGCCTTCCGGATG	TCCCCAAGTGTGACA
	GACTCCCTGCCAACA	GCGCCTTCCGGATGA	CCCCAAGTGTGACAA
	ACTCCCTGCCAACAG	CGCCTTCCGGATGAG	CCCAACTGTGACAAG
50	CTCCCTGCCAACAGG	GCCTTCCGGATGAGC	CCAAGTGTGACAAGC
	TCCCTGCCAACAGGA	CCTTCCGGATGAGCG	CAAGTGTGACAAGCA

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AACTGTGACAAGCAT	AACGGGCAGCGTGGG	ATCCAGGGAGCCCCC
ACTGTGACAAGCATG	ACGGGCAGCGTGGGG	TCCAGGGAGCCCCCA
CTGTGACAAGCATGG	CGGGCAGCGTGGGGA	CCAGGGAGCCCCCAC
TGTGACAAGCATGGC	GGGCAGCGTGGGGAG	CAGGGAGCCCCCACC
5 GTGACAAGCATGGCC	GGCAGCGTGGGGAGT	AGGGAGCCCCCACCA
TGACAAGCATGGCCT	GCAGCGTGGGGAGTG	GGGAGCCCCCACCAT
GACAAGCATGGCCTG	CAGCGTGGGGAGTGC	GGAGCCCCCACCATC
ACAAGCATGGCCTGT	AGCGTGGGGAGTGCT	GAGCCCCCACCATCC
CAAGCATGGCCTGTA	GCGTGGGGAGTGCTG	AGCCCCCACCATCCG
10 AAGCATGGCCTGTAC	CGTGGGGAGTGCTGG	GCCCCCACCATCCGG
AGCATGGCCTGTACA	GTGGGGAGTGCTGGT	CCCCCACCATCCGGG
GCATGGCCTGTACAA	TGGGGAGTGCTGGTG	CCCCCACCATCCGGGG
CATGGCCTGTACAAC	GGGGAGTGCTGGTGT	CCCACCATCCGGGGG
ATGGCCTGTACAACC	GGGAGTGCTGGTGTG	CCACCATCCGGGGGG
15 TGGCCTGTACAACCT	GGAGTGCTGGTGTGT	CACCATCCGGGGGGGA
GGCCTGTACAACCTC	GAGTGCTGGTGTGTG	ACCATCCGGGGGGGAC
GCCTGTACAACCTCA	AGTGCTGGTGTGTGA	CCATCCGGGGGGGACC
CCTGTACAACCTCAA	GTGCTGGTGTGTGAA	CATCCGGGGGGGACCC
CTGTACAACCTCAAA	TGCTGGTGTGTGAAC	ATCCGGGGGGGACCCC
20 TGTACAACCTCAAAC	GCTGGTGTGTGAACC	TCCGGGGGGGACCCCC
GTACAACCTCAAACA	CTGGTGTGTGAACCC	CCGGGGGGGACCCCCA
TACAACCTCAAACAG	TGGTGTGTGAACCCC	CGGGGGGACCCCCGAG
ACAACCTCAAACAGT	GGTGTGTGAACCCCA	GGGGGGACCCCCGAGT
CAACCTCAAACAGTG	GTGTGTGAACCCCAA	GGGGGACCCCCGAGTG
25 AACCTCAAACAGTGC	TGTGTGAACCCCAAC	GGGGACCCCCGAGTGT
ACCTCAAACAGTGCA	GTGTGAACCCCAACA	GGGACCCCCGAGTGTC
CCTCAAACAGTGCAA	TGTGAACCCCAACAC	GGACCCCCGAGTGTCAT
CTCAAACAGTGCAAG	GTGAACCCCAACACC	GACCCCCGAGTGTCATC
TCAAACAGTGCAAGA	TGAACCCCAACACCG	ACCCCCGAGTGTCATCT
30 CAAACAGTGCAAGAT	GAACCCCAACACCGG	CCCCGAGTGTCATCTC
AAACAGTGCAAGATG	AACCCCAACACCGGG	CCCGAGTGTCATCTCT
AACAGTGCAAGATGT	ACCCCAACACCGGGA	CCGAGTGTCATCTCTT
ACAGTGCAAGATGTC	CCCCAACACCGGGAA	CGAGTGTCATCTCTTT
CAGTGCAAGATGTCT	CCCAACACCGGGAAG	GAGTGTCATCTCTTCT
35 AGTGCAAGATGTCTC	CCAACACCGGGAAGC	AGTGTCATCTCTTCTA
GTGCAAGATGTCTCT	CAACACCGGGAAGCT	GTGTCATCTCTTCTAC
TGCAAGATGTCTCTG	AACACCGGGAAGCTG	GTCATCTCTTCTACAA
GCAAGATGTCTCTGA	ACACCGGGAAGCTGAT	TCATCTCTTCTACAAT
CAAGATGTCTCTGAA	ACCGGGAAGCTGATC	CATCTCTTCTACAATG
40 AAGATGTCTCTGAAC	CCGGGAAGCTGATCC	ATCTCTTCTACAATGA
AGATGTCTCTGAACG	CGGGAAGCTGATCCA	TCTCTTCTACAATGAG
GATGTCTCTGAACGG	GGAAGCTGATCCAG	TCTTCTACAATGAGC
ATGTCTCTGAACGGG	GAAGCTGATCCAGG	CTTCTACAATGAGCA
TGTCTCTGAACGGGC	AAGCTGATCCAGGGA	TTCTACAATGAGCAG
45 GTCTCTGAACGGGCA	AGCTGATCCAGGGAG	TCTACAATGAGCAGC
TCTCTGAACGGGCAG	GCTGATCCAGGGAGC	CTACAATGAGCAGCA
CTCTGAACGGGCAGC	CTGATCCAGGGAGCC	TACAATGAGCAGCAG
TCTGAACGGGCAGCG	TGATCCAGGGAGCCC	ACAATGAGCAGCAGG
CTGAACGGGCAGCGT	GATCCAGGGAGCCCC	CAATGAGCAGCAGGA
50 TGAACGGGCAGCGTG		
GAACGGGCAGCGTGG		

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AATGAGCAGCAGGAG	GCAGCCAGCCGGTGC	GCAGAAAACGGAGAG
ATGAGCAGCAGGAGG	CAGCCAGCCGGTGCC	CAGAAAACGGAGAGT
TGAGCAGCAGGAGGC	AGCCAGCCGGTGCCCT	AGAAAACGGAGAGTG
GAGCAGCAGGAGGCT	GCCAGCCGGTGCCCTG	GAAAACGGAGAGTGCT
5 AGCAGCAGGAGGCTT	CCAGCCGGTGCCCTGG	AAAACGGAGAGTGCTT
GCAGCAGGAGGCTTG	CAGCCGGTGCCCTGGC	AAACGGAGAGTGCTTG
CAGCAGGAGGCTTGC	AGCCGGTGCCCTGGCG	ACGGAGAGTGCTTGG
AGCAGGAGGCTTGCG	GCCGGTGCCCTGGCGC	ACGGAGAGTGCTTGGG
GCAGGAGGCTTGCGG	CCGGTGCCCTGGCGCC	CGGAGAGTGCTTGGG
10 CAGGAGGCTTGCGGG	CGGTGCCTGGCGCCC	GGAGAGTGCTTGGGT
AGGAGGCTTGCGGGG	GGTGCCTGGCGCCCC	GAGAGTGCTTGGGTG
GGAGGCTTGCGGGGT	GTGCCTGGCGCCCCCT	AGAGTGCTTGGGTGG
GAGGCTTGCGGGGTG	TGCCTGGCGCCCCCTG	GAGTGCTTGGGTGGT
AGGCTTGCGGGGTGC	GCCTGGCGCCCCCTGC	AGTGCTTGGGTGGTG
15 GGCTTGCGGGGTGCA	CCTGGCGCCCCCTGCC	GTGCTTGGGTGGTGG
GCTTGCGGGGTGCAC	CTGGCGCCCCCTGCCC	TGCTTGGGTGGTGGG
CTTGCGGGGTGCACA	TGGCGCCCCCTGCCCC	GCTTGGGTGGTGGGT
TTGCGGGGTGCACAC	GGCGCCCCCTGCCCCC	CTTGGGTGGTGGGTG
TGCGGGGTGCACACC	GCGCCCCCTGCCCCC	TTGGGTGGTGGGTGC
20 GCGGGGTGCACACCC	CGCCCCCTGCCCCCG	TGGGTGGTGGGTGCT
CGGGGTGCACACCCA	GCCCCCTGCCCCCGC	GGGTGGTGGGTGCTG
GGGGTGCACACCCAG	CCCCTGCCCCCGCC	GGTGGTGGGTGCTGG
GGGTGCACACCCAGC	CCCTGCCCCCGCCC	GTGGTGGGTGCTGGA
GGTGCACACCCAGCG	CCTGCCCCCGCCCC	TGGTGGGTGCTGGAG
25 GTGCACACCCAGCGG	CTGCCCCCGCCCCCT	GGTGGGTGCTGGAGG
TGCACACCCAGCGGA	TGCCCCCGCCCCCTC	GTGGGTGCTGGAGGA
GCACACCCAGCGGAT	GCCCCCGCCCCCTCT	TGGGTGCTGGAGGAT
CACACCCAGCGGATG	CCCCCGCCCCCTCTC	GGGTGCTGGAGGATT
ACACCCAGCGGATGC	CCCCCGCCCCCTCTCC	GGTGCTGGAGGATTT
30 CACCCAGCGGATGCA	CCCCGCCCCCTCTCCA	GTGCTGGAGGATTTT
ACCCAGCGGATGCAG	CCCGCCCCCTCTCCAA	TGCTGGAGGATTTTC
CCCAGCGGATGCAGT	CCGCCCCCTCTCCAAA	GCTGGAGGATTTTCC
CCAGCGGATGCAGTA	CGCCCCCTCTCCAAAC	CTGGAGGATTTTCCA
CAGCGGATGCAGTAG	GCCCCCTCTCCAAACA	TGGAGGATTTTCCAG
35 AGCGGATGCAGTAGA	CCCCTCTCCAAACAC	GGAGGATTTTCCAGT
GCGGATGCAGTAGAC	CCCTCTCCAAACACC	GAGGATTTTCCAGTT
CGGATGCAGTAGACC	CCTCTCCAAACACCG	AGGATTTTCCAGTTC
GGATGCAGTAGACCG	CTCTCCAAACACCGG	GGATTTTCCAGTTCT
GATGCAGTAGACCGC	TCTCCAAACACCGGC	GATTTTCCAGTTCTG
40 ATGCAGTAGACCGCA	CTCCAAACACCGGCA	ATTTTCCAGTTCTGA
TGCAGTAGACCGCAG	TCCAAACACCGGCAG	TTTTCCAGTTCTGAC
GCAGTAGACCGCAGC	CCAAACACCGGCAGA	TTTCCAGTTCTGACA
CAGTAGACCGCAGCC	CAAACACCGGCAGAA	TTCCAGTTCTGACAC
AGTAGACCGCAGCCA	AAACACCGGCAGAAA	TCCAGTTCTGACACA
45 GTAGACCGCAGCCAG	AACACCGGCAGAAAA	CCAGTTCTGACACAC
TAGACCGCAGCCAGC	ACACCGGCAGAAAAC	CAGTTCTGACACACG
AGACCGCAGCCAGCC	CACCGGCAGAAAACG	AGTTCTGACACACGT
GACCGCAGCCAGCCG	ACCGGCAGAAAACGG	GTTCTGACACACGTA
ACCGCAGCCAGCCGG	CCGGCAGAAAACGGA	TTCTGACACACGTAT
50 CCGCAGCCAGCCGGT	CGGCAGAAAACGGAG	TCTGACACACGTATT
CGCAGCCAGCCGGTG	GGCAGAAAACGGAGA	CTGACACACGTATTT

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5	TGACACACGTATTTA GACACACGTATTTAT ACACACGTATTTATA CACACGTATTTATAT ACACGTATTTATATT CACGTATTTATATTT ACGTATTTATATTTG CGTATTTATATTTGG GTATTTATATTTGGA	CCCCGGCCTCTCTCTT CCGGCCTCTCTCTTC CGGCCTCTCTCTTCC GGCCTCTCTCTTCCC GCCTCTCTCTTCCCA CCTCTCTCTTCCCAG CTCTCTCTTCCCAGC TCTCTCTTCCCAGCT CTCTCTTCCCAGCTG TCTCTTCCCAGCTGC CTCTTCCCAGCTGCA TCTTCCCAGCTGCAG CTTCCCAGCTGCAGA TTCCCAGCTGCAGAT TCCCAGCTGCAGATG CCCAGCTGCAGATGC CCAGCTGCAGATGCC CAGCTGCAGATGCCA AGCTGCAGATGCCAC GCTGCAGATGCCACA CTGCAGATGCCACAC TGCAGATGCCACACC GCAGATGCCACACCT CAGATGCCACACCTG AGATGCCACACCTGC GATGCCACACCTGCT ATGCCACACCTGCTC TGCCACACCTGCTCC GCCACACCTGCTCCT CCACACCTGCTCCTT CACACCTGCTCCTTC ACACCTGCTCCTTCT CACCTGCTCCTTCTT ACCTGCTCCTTCTTG CCTGCTCCTTCTTGC CTGCTCCTTCTTGCT TGCTCCTTCTTGCTT GCTCCTTCTTGCTTT CTCCTTCTTGCTTTC TCCTTCTTGCTTTCC CCTTCTTGCTTTCCC CTTCTTGCTTTCCCC TTCTTGCTTTCCCCG TCTTGCTTTCCCCGG CTTGCTTTCCCCGGG TTGCTTTCCCCGGGG TGCTTTCCCCGGGGG GCTTTCCCCGGGGGA CTTTCCCCGGGGGAG TTTCCCCGGGGGAGG TTCCCCGGGGGAGGA	TCCCCGGGGGAGGAA CCCCGGGGGAGGAAG CCCCGGGGGAGGAAGG CCGGGGGAGGAAGGG CGGGGGAGGAAGGGG GGGGGAGGAAGGGGG GGGGAGGAAGGGGGT GGGAGGAAGGGGGTT GGAGGAAGGGGGTTG GAGGAAGGGGGTTGT AGGAAGGGGGTTGTG GGAAGGGGGTTGTGG GAAGGGGGTTGTGGT AAGGGGGTTGTGGTC AGGGGGTTGTGGTCG GGGGTTGTGGTCGG GGGTTGTGGTCGGGG GGTTGTGGTCGGGGA GTTGTGGTCGGGGAG TTGTGGTCGGGGAGC TGTGGTCGGGGAGCT GTGGTCGGGGAGCTG TGGTCGGGGAGCTGG GGTCGGGGAGCTGGG GTCGGGGAGCTGGGG TCGGGGAGCTGGGGT CGGGGAGCTGGGGTA GGGGAGCTGGGGTACA GGAGCTGGGGTACAG GAGCTGGGGTACAGG AGCTGGGGTACAGGT GCTGGGGTACAGGTT CTGGGGTACAGGTTT TGGGGTACAGGTTTG GGGGTACAGGTTTGG GGGTACAGGTTTGGG GGTACAGGTTTGGGG GTACAGGTTTGGGGA TACAGGTTTGGGGAG ACAGGTTTGGGGAGG CAGGTTTGGGGAGGG AGGTTTGGGGAGGGG GGTTTGGGGAGGGGG GTTTGGGGAGGGGGA TTTGGGGAGGGGGA TTGGGGAGGGGGAAG TGGGGAGGGGGAAGA GGGGAGGGGGAAGAG GGGAGGGGGAAGAGA
10	TATTTATATTTGGAA ATTTATATTTGGAAA TTTATATTTGGAAAG TTATATTTGGAAAGA TATATTTGGAAAGAG		
15	ATATTTGGAAAGAGA TATTTGGAAAGAGAC ATTTGGAAAGAGACC TTTGGAAAGAGACCA TTGGAAAGAGACCAG		
20	TGGAAAGAGACCAGC GGAAAGAGACCAGCA GAAAGAGACCAGCAC AAAGAGACCAGCACC AAGAGACCAGCACCG		
25	AGAGACCAGCACCGA GAGACCAGCACCGAG AGACCAGCACCGAGC GACCAGCACCGAGCT ACCAGCACCGAGCTC		
30	CCAGCACCGAGCTCG CAGCACCGAGCTCGG AGCACCGAGCTCGGC GCACCGAGCTCGGCA CACCGAGCTCGGCAC		
35	ACCGAGCTCGGCACC CCGAGCTCGGCACCT CGAGCTCGGCACCTC GAGCTCGGCACCTCC AGCTCGGCACCTCCC		
40	GCTCGGCACCTCCCC CTCGGCACCTCCCCG TCGGCACCTCCCCGG CGGCACCTCCCCGGC GGCACCTCCCCGGCC		
45	GCACCTCCCCGGCCT CACCTCCCCGGCCTC ACCTCCCCGGCCTCT CCTCCCCGGCCTCTC CTCCCCGGCCTCTCT		
50	TCCCCGGCCTCTCTC CCCCGGCCTCTCTCT		

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	GGAGGGGGAAGAGAA	AGATTAAAGGAAGGA
	GAGGGGGAAGAGAAA	GATTAAAGGAAGGAA
	AGGGGGAAGAGAAAT	ATTAAAGGAAGGAAA
	GGGGGAAGAGAAATT	TTAAAGGAAGGAAAA
5	GGGGAAGAGAAATTT	TAAAGGAAGGAAAAG
	GGGAAGAGAAATTTT	AAAGGAAGGAAAAGT
	GGAAGAGAAATTTTT	
	GAAGAGAAATTTTTA	
	AAGAGAAATTTTTAT	
10	AGAGAAATTTTTATT	
	GAGAAATTTTTATTT	
	AGAAATTTTTATTTT	
	GAAATTTTTATTTT	
	AAATTTTTATTTTG	
15	AATTTTTATTTTGA	
	ATTTTTATTTTGAA	
	TTTTTATTTTGAAC	
	TTTTATTTTGAACC	
	TTTATTTTGAACCC	
20	TTATTTTGAACCCC	
	TATTTTGAACCCCT	
	ATTTTGAACCCCTG	
	TTTTTGAACCCCTGT	
	TTTTGAACCCCTGTG	
25	TTTGAACCCCTGTGT	
	TTGAACCCCTGTGTC	
	TGAACCCCTGTGTCC	
	GAACCCCTGTGTCCC	
	AACCCCTGTGTCCCT	
30	ACCCCTGTGTCCCTT	
	CCCCTGTGTCCCTTT	
	CCCTGTGTCCCTTTT	
	CCTGTGTCCCTTTTG	
	CTGTGTCCCTTTTGC	
35	TGTGTCCCTTTTGCA	
	GTGTCCCTTTTGCAT	
	TGTCCCTTTTGCATA	
	GTCCCTTTTGCATAA	
	TCCCTTTTGCATAAG	
40	CCCTTTTGCATAAGA	
	CCTTTTGCATAAGAT	
	CTTTTGCATAAGATT	
	TTTTGCATAAGATTA	
	TTTGCATAAGATTAA	
45	TTGCATAAGATTAAA	
	TGCATAAGATTAAAG	
	GCATAAGATTAAAGG	
	CATAAGATTAAAGGA	
	ATAAGATTAAAGGAA	
50	TAAGATTAAAGGAAG	
	AAGATTAAAGGAAGG	



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## EXAMPLE 7

Antisense oligonucleotides to IGFBP3 may be selected from molecules capable of interacting

5 with one or more of the following sense oligonucleotides:

CTCAGCGCCCAGCCG	GCCGTGTACTGTTCGC	GCAGCGTGCCCCGGT
TCAGCGCCCAGCCGC	CCGTGTACTGTTCGCC	CAGCGTGCCCCGGTT
CAGCGCCCAGCCGCT	CGTGTACTGTTCGCCC	AGCGTGCCCCGGTTG
10 AGCGCCCAGCCGCTT	GTGTACTGTTCGCCCC	GCGTGCCCCGGTTGC
GCGCCCAGCCGCTTC	TGTACTGTTCGCCCCA	CGTGCCCCGGTTGCA
CGCCCAGCCGCTTCC	GTACTGTTCGCCCCAT	GTGCCCCGGTTGCAG
GCCCAGCCGCTTCCT	TACTGTTCGCCCCATC	TGCCCCGGTTGCAGG
CCCAGCCGCTTCCTG	ACTGTTCGCCCCATCC	GCCCCGGTTGCAGGC
15 CCAGCCGCTTCCTGC	CTGTTCGCCCCATCCC	CCCCGGTTGCAGGCG
CAGCCGCTTCCTGCC	TGTTCGCCCCATCCCT	CCCGGTTGCAGGCGT
AGCCGCTTCCTGCCT	GTTCGCCCCATCCCTG	CCGGTTGCAGGCGTC
GCCGCTTCCTGCCTG	TCGCCCCATCCCTGC	CGGTTGCAGGCGTCA
CCGCTTCCTGCCTGG	CGCCCCATCCCTGCG	GGTTGCAGGCGTCAT
20 CGCTTCCTGCCTGGA	GCCCCATCCCTGCGC	GTTGCAGGCGTCATG
GCTTCCTGCCTGGAT	CCCCATCCCTGCGCG	TTGCAGGCGTCATGC
CTTCCTGCCTGGATT	CCCATCCCTGCGCGC	TGCAGGCGTCATGCA
TTCCTGCCTGGATTCC	CCATCCCTGCGCGCC	GCAGGCGTCATGCAG
TCCTGCCTGGATTCC	CATCCCTGCGCGCCC	CAGGCGTCATGCAGC
25 CCTGCCTGGATTCCA	ATCCCTGCGCGCCCA	AGGCGTCATGCAGCG
CTGCCTGGATTCCAC	TCCCTGCGCGCCCAG	GGCGTCATGCAGCGG
TGCCTGGATTCCACA	CCCTGCGCGCCCAGC	GCGTCATGCAGCGGG
GCCTGGATTCCACAG	CCTGCGCGCCCAGCC	CGTCATGCAGCGGGC
CCTGGATTCCACAGC	CTGCGCGCCCAGCCT	GTCATGCAGCGGGCG
30 CTGGATTCCACAGCT	TGCGCGCCCAGCCTG	TCATGCAGCGGGCGC
TGGATTCCACAGCTT	GCGCGCCCAGCCTGC	CATGCAGCGGGCGCG
GGATTCCACAGCTTC	CGCGCCCAGCCTGCC	ATGCAGCGGGCGCGA
GATTCCACAGCTTCG	GCGCCCAGCCTGCCA	TGCAGCGGGCGCGAC
ATTCCACAGCTTCGC	CGCCCAGCCTGCCAA	GCAGCGGGCGCGACC
35 TTCCACAGCTTCGCG	GCCCAGCCTGCCAAG	CAGCGGGCGCGACCC
TCCACAGCTTCGCGC	CCCAGCCTGCCAAGC	AGCGGGCGCGACCCA
CCACAGCTTCGCGCC	CCAGCCTGCCAAGCA	GCGGGCGCGACCCAC
CACAGCTTCGCGCCG	CAGCCTGCCAAGCAG	CGGGCGCGACCCACG
ACAGCTTCGCGCCGT	AGCCTGCCAAGCAGC	GGGCGCGACCCACGCT
40 CAGCTTCGCGCCGTG	GCCTGCCAAGCAGCG	GCGCGACCCACGCTC
AGCTTCGCGCCGTGT	CCTGCCAAGCAGCGT	CGCGACCCACGCTCT
GCTTCGCGCCGTGTA	CTGCCAAGCAGCGTG	GCGACCCACGCTCTG
CTTCGCGCCGTGTAC	TGCCAAGCAGCGTGC	CGACCCACGCTCTGG
TTCGCGCCGTGTACT	GCCAAGCAGCGTGCC	GACCCACGCTCTGGG
45 TCGCGCCGTGTACTG	CCAAGCAGCGTGCCC	ACCCACGCTCTGGGC
CGCGCCGTGTACTGT	CAAGCAGCGTGCCCC	CCCACGCTCTGGGCC
GCGCCGTGTACTGTC	AAGCAGCGTGCCCCG	CCACGCTCTGGGCCG
CGCCGTGTACTGTTCG	AGCAGCGTGCCCCGG	

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CACGCTCTGGGCCGC	GGTGGCGCGGGCTGG	CGAGCCGTGCGACGC
ACGCTCTGGGCCGCT	GTGGCGCGGGCTGGC	GAGCCGTGCGACGCG
CGCTCTGGGCCGCTG	TGGCGCGGGCTGGCG	AGCCGTGCGACGCGC
GCTCTGGGCCGCTGC	GGCGCGGGCTGGCGC	GCCGTGCGACGCGCG
5 CTCTGGGCCGCTGCG	GCGCGGGCTGGCGCG	CCGTGCGACGCGCGT
TCTGGGCCGCTGCGC	CGCGGGCTGGCGCGA	CGTGCGACGCGCGTG
CTGGGCCGCTGCGCT	GCGGGCTGGCGCGAG	GTGCGACGCGCGTG
TGGGCCGCTGCGCTG	CGGGCTGGCGCGAGC	TGCGACGCGCGTGCA
GGGCCGCTGCGCTGA	GGGCTGGCGCGAGCT	GCGACGCGCGTGCA
10 GGCCGCTGCGCTGAC	GGCTGGCGCGAGCTC	CGACGCGCGTGCACT
GCCGCTGCGCTGACT	GCTGGCGCGAGCTCG	GACGCGCGTGCACTG
CCGCTGCGCTGACTC	CTGGCGCGAGCTCGG	ACGCGCGTGCACTGG
CGCTGCGCTGACTCT	TGGCGCGAGCTCGGG	CGCGCGTGCACTGGC
GCTGCGCTGACTCTG	GGCGCGAGCTCGGGG	GCGCGTGCACTGGCC
15 CTGCGCTGACTCTGC	GCGCGAGCTCGGGGG	CGCGTGCACTGGCCC
TGCGCTGACTCTGCT	CGCGAGCTCGGGGGG	GCGTGCACTGGCCCCA
GCGCTGACTCTGCTG	GCGAGCTCGGGGGGC	CGTGCACTGGCCCCAG
CGCTGACTCTGCTGG	CGAGCTCGGGGGGCT	GTGCACTGGCCCCAGT
GCTGACTCTGCTGGT	GAGCTCGGGGGGCTT	TGCACTGGCCCCAGTG
20 CTGACTCTGCTGGTG	AGCTCGGGGGGCTTG	GCACTGGCCCCAGTGC
TGACTCTGCTGGTG	GCTCGGGGGGCTTGG	CACTGGCCCCAGTGCG
GACTCTGCTGGTGCT	CTCGGGGGGCTTGGG	ACTGGCCCCAGTGCGC
ACTCTGCTGGTGCTG	TCGGGGGGGCTTGGGT	CTGGCCCCAGTGCGCG
CTCTGCTGGTGCTGC	CGGGGGGCTTGGGTC	TGGCCCCAGTGCGCGC
25 TCTGCTGGTGCTGCT	GGGGGGGCTTGGGTCC	GGCCCCAGTGCGCGCC
CTGCTGGTGCTGCTC	GGGGGCTTGGGTCCC	GCCCCAGTGCGCGCCT
TGCTGGTGCTGCTCC	GGGGCTTGGGTCCCG	CCCAGTGCGCGCCTC
GCTGGTGCTGCTCCG	GGGCTTGGGTCCCGT	CCAGTGCGCGCCTCC
CTGGTGCTGCTCCGC	GGCTTGGGTCCCGTG	CAGTGCGCGCCTCCG
30 TGGTGCTGCTCCGCG	GCTTGGGTCCCGTGG	AGTGCGCGCCTCCGC
GGTGCTGCTCCGCGG	CTTGGGTCCCGTGGT	GTGCGCGCCTCCGCC
GTGCTGCTCCGCGGG	TTGGGTCCCGTGGTG	TGCGCGCCTCCGCCC
TGCTGCTCCGCGGGC	TGGGTCCCGTGGTG	GCGCGCCTCCGCCCC
GCTGCTCCGCGGGCC	GGGTCCCGTGGTGCG	CGCGCCTCCGCCCCG
35 CTGCTCCGCGGGCCG	GGTCCCGTGGTGCGC	GCGCCTCCGCCCCG
TGCTCCGCGGGCCCG	GTCCCGTGGTGCGCT	CGCCTCCGCCCCGCG
GCTCCGCGGGCCCGC	TCCCGTGGTGCGCTG	GCCTCCGCCCCGCGT
CTCCGCGGGCCCGCG	CCCCTGGTGCGCTGC	CCTCCGCCCCGCGTG
TCCGCGGGCCCGCGG	CCGTGGTGCGCTGCG	CTCCGCCCCGCGTGT
40 CCGCGGGCCCGCCGGT	CGTGGTGCGCTGCGA	TCCGCCCCGCGTGTG
CGCGGGCCCGCCGGTG	GTGGTGCGCTGCGAG	CCGCCCCGCGTGTGC
GCGGGCCCGCCGGTGG	TGGTGCGCTGCGAGC	CGCCCCGCGTGTGCG
CGGGCCCGCCGGTGGC	GGTGCGCTGCGAGCC	GCCCCGCGTGTGCGC
GGGCCCGCCGGTGGCG	GTGCGCTGCGAGCCG	CCCGCCGTGTGCGCG
45 GGCCCGCCGGTGGCGC	TGCGCTGCGAGCCGT	CCGCCGTGTGCGCGG
GCCGCCGGTGGCGCG	GCGCTGCGAGCCGTG	CGCCGTGTGCGCGGA
CCGCCGGTGGCGCGG	CGCTGCGAGCCGTGC	GCCGTGTGCGCGGAG
CGCCGGTGGCGCGGG	GCTGCGAGCCGTGCG	CCGTGTGCGCGGAGC
GCCGGTGGCGCGGGC	CTGCGAGCCGTGCGA	CGTGTGCGCGGAGCT
50 CCGGTGGCGCGGGCT	TGCGAGCCGTGCGAC	GTGTGCGCGGAGCTG
CGGTGGCGCGGGCTG	GCGAGCCGTGCGACG	TGTGCGCGGAGCTGG

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GTGCGCGGAGCTGGT	ACTGAGCGAGGGCCA	CCTTCGCTGCCAGCC
TGCGCGGAGCTGGTG	CTGAGCGAGGGCCAG	CTTCGCTGCCAGCCG
GCGCGGAGCTGGTG	TGAGCGAGGGCCAGC	TTCGCTGCCAGCCGT
CGCGGAGCTGGTGCG	GAGCGAGGGCCAGCC	TCGCTGCCAGCCGTC
5 GCGGAGCTGGTGCGC	AGCGAGGGCCAGCCG	CGCTGCCAGCCGTGC
CGGAGCTGGTGCGCG	GCGAGGGCCAGCCGT	GCTGCCAGCCGTGCG
GGAGCTGGTGCGCGA	CGAGGGCCAGCCGTG	CTGCCAGCCGTGCCC
GAGCTGGTGCGCGAG	GAGGGCCAGCCGTGC	TGCCAGCCGTGCCCC
AGCTGGTGCGCGAGC	AGGGCCAGCCGTGCG	GCCAGCCGTGCCCCG
10 GCTGGTGCGCGAGCC	GGGCCAGCCGTGCGG	CCAGCCGTGCCCCGA
CTGGTGCGCGAGCCG	GGCCAGCCGTGCGGC	CAGCCGTGCCCCGAC
TGGTGCGCGAGCCGG	GCCAGCCGTGCGGCA	AGCCGTGCCCCGACG
GGTGCGCGAGCCGGG	CCAGCCGTGCGGCAT	GCCGTGCCCCGACGA
GTGCGCGAGCCGGGC	CAGCCGTGCGGCATC	CCGTGCCCCGACGAG
15 TGCGCGAGCCGGGCT	AGCCGTGCGGCATCT	CGTCGCCCCGACGAGG
GCGCGAGCCGGGCTG	GCCGTGCGGCATCTA	GTGCCCCGACGAGGC
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25 GGGCTGCGGCTGCTG	CATCTACACCGAGCG	CGAGGCGCGACCCGT
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CCTACCTGCTGCCAG	AAGACCGCAGCGCCG	

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50 AAGAAAGGGCATGCT	CAGAGCACAGATACC	TATGGTCCCTGCCGT
AGAAAGGGCATGCTA	AGAGCACAGATACCC	ATGGTCCCTGCCGTA

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5	TGGTCCCTGCCGTAG GGTCCCTGCCGTAGA GTCCCTGCCGTAGAG TCCCTGCCGTAGAGA CCCTGCCGTAGAGAA CCTGCCGTAGAGAAA CTGCCGTAGAGAAAT TGCCGTAGAGAAATG GCCGTAGAGAAATGG 10 CCGTAGAGAAATGGA CGTAGAGAAATGGAA GTAGAGAAATGGAAG TAGAGAAATGGAAGA AGAGAAATGGAAGAC 15 GAGAAATGGAAGACA AGAAATGGAAGACAC GAAATGGAAGACACA AAATGGAAGACACAC AATGGAAGACACACT 20 ATGGAAGACACACTG TGGAAGACACACTGA GGAAGACACACTGAA GAAGACACACTGAAT AAGACACACTGAATC 25 AGACACACTGAATCA GACACACTGAATCAC ACACACTGAATCACC CACACTGAATCACCT ACACTGAATCACCTG 30 CACTGAATCACCTGA ACTGAATCACCTGAA CTGAATCACCTGAAG TGAATCACCTGAAGT GAATCACCTGAAGTT 35 AATCACCTGAAGTTC ATCACCTGAAGTTCC TCACCTGAAGTTCCT CACCTGAAGTTCCTC ACCTGAAGTTCCTCA 40 CCTGAAGTTCCTCAA CTGAAGTTCCTCAAT TGAAGTTCCTCAATG GAAGTTCCTCAATGT AAGTTCCTCAATGTG 45 AGTTCTCAATGTGC GTTCTCAATGTGCT TTCCTCAATGTGCTG TCCTCAATGTGCTGA CCTCAATGTGCTGAG 50 CTCAATGTGCTGAGT TCAATGTGCTGAGTC	CAATGTGCTGAGTCC AATGTGCTGAGTCCC ATGTGCTGAGTCCCA TGTGCTGAGTCCCAG GTGCTGAGTCCCAGG TGCTGAGTCCCAGGG GCTGAGTCCCAGGGG CTGAGTCCCAGGGGT TGAGTCCCAGGGGTG GAGTCCCAGGGGTGT AGTCCCAGGGGTGTA GTCCCAGGGGTGTAC TCCCAGGGGTGTACA CCCAGGGGTGTACAC CCAGGGGTGTACACA CAGGGGTGTACACAT AGGGGTGTACACATT GGGGTGTACACATTC GGGTGTACACATTCC GGTGTACACATTCCC GTGTACACATTCCCA TGTACACATTCCCAA GTACACATTCCCAAC TACACATTCCCAACT ACACATTCCCAACTG CACATTCCCAACTGT ACATTCCCAACTGTG CATTCCCAACTGTGA ATTCCCAACTGTGAC TTCCCAACTGTGACA TCCCAACTGTGACAA CCCAACTGTGACAAG CCAAGTGTGACAAGA CAACTGTGACAAGAA AACTGTGACAAGAAG ACTGTGACAAGAAGG CTGTGACAAGAAGGG TGTGACAAGAAGGGA GTGACAAGAAGGGAT TGACAAGAAGGGATT GACAAGAAGGGATTT ACAAGAAGGGATTTT CAAGAAGGGATTTTA AAGAAGGGATTTTAT AGAAGGGATTTTATA GAAGGGATTTTATAA AAGGGATTTTATAAG AGGGATTTTATAAGA GGGATTTTATAAGAA GGATTTTATAAGAAA GATTTTATAAGAAAA	ATTTTATAAGAAAAA TTTTATAAGAAAAAG TTTATAAGAAAAAGC TTATAAGAAAAAGCA TATAAGAAAAAGCAG ATAAGAAAAAGCAGT TAAGAAAAAGCAGTG AAGAAAAAGCAGTGT AGAAAAAGCAGTGTG GAAAAAGCAGTGTGCG AAAAAGCAGTGTGCGC AAAAGCAGTGTGCGCC AAAGCAGTGTGCGCCC AAGCAGTGTGCGCCCT AGCAGTGTGCGCCCTT GCAGTGTGCGCCCTTC CAGTGTGCGCCCTTCC AGTGTGCGCCCTTCCA GTGTGCGCCCTTCCAA TGTGCGCCCTTCCAAA GTCGCCCTTCCAAAG TCGCCCTTCCAAAGG CGCCCTTCCAAAGGC GCCCTTCCAAAGGCA CCCTTCCAAAGGCAG CCTTCCAAAGGCAGG CTTCCAAAGGCAGGA TTCCAAAGGCAGGAA TCCAAAGGCAGGAAG CCAAAGGCAGGAAGC CAAAGGCAGGAAGCG AAAGGCAGGAAGCGG AAGGCAGGAAGCGGG AGGCAGGAAGCGGGG GGCAGGAAGCGGGGC GCAGGAAGCGGGGCT CAGGAAGCGGGGCTT AGGAAGCGGGGCTTC GGAAGCGGGGCTTCT GAAGCGGGGCTTCTG AAGCGGGGCTTCTGC AGCGGGGCTTCTGCT GCGGGGCTTCTGCTG CGGGGCTTCTGCTGG GGGGCTTCTGCTGGT GGCTTCTGCTGGTGT GCTTCTGCTGGTGTG CTTCTGCTGGTGTGT TTCTGCTGGTGTGTG TCTGCTGGTGTGTGG
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35 TATCAAAAATATTCAG	GGAATGCTCACCACA	TAGGCGGCTGTGTTG
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50 AGACTCGAGCACAGC	TGTTGGTCGAAGCGG	CCTATGTAGAGAAC
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50 TTTATCGAGAATAGG	CATGCTCCTGGAGCT	GTGGAT
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5	TGGATCCCTCAACCA GGATCCCTCAACCAA GATCCCTCAACCAAG ATCCCTCAACCAAGA TCCCTCAACCAAGAA CCCTCAACCAAGAAG CCTCAACCAAGAAGA CTCAACCAAGAAGAA TCAACCAAGAAGAAT CAACCAAGAAGAATG AACCAAGAAGAATGT ACCAAGAAGAATGTT CCAAGAAGAATGTTT CAAGAAGAATGTTTA AAGAAGAATGTTTAT AGAAGAATGTTTATG GAAGAATGTTTATGT AAGAATGTTTATGTC AGAATGTTTATGTCT GAATGTTTATGTCTT AATGTTTATGTCTTC ATGTTTATGTCTTCA TGTTTATGTCTTCAA GTTTATGTCTTCAAG TTTATGTCTTCAAGT TTATGTCTTCAAGTG TATGTCTTCAAGTGA ATGTCTTCAAGTGAC TGTCTTCAAGTGACC GTCTTCAAGTGACCT TCTTCAAGTGACCTG CTTCAAGTGACCTGT TTCAAGTGACCTGTA TCAAGTGACCTGTAC CAAGTGACCTGTACT AAGTGACCTGTACTG AGTGACCTGTACTGC GTGACCTGTACTGCT TGACCTGTACTGCTT GACCTGTACTGCTTG ACCTGTACTGCTTGG CCTGTACTGCTTGGG CTGTACTGCTTGGGG TGTACTGCTTGGGGA GTACTGCTTGGGGAC TACTGCTTGGGGACT ACTGCTTGGGGACTA CTGCTTGGGGACTAT TGCTTGGGGACTATT GCTTGGGGACTATTG CTTGGGGACTATTGG	TTGGGGACTATTGGA TGGGGACTATTGGAG GGGGACTATTGGAGA GGGACTATTGGAGAA GGACTATTGGAGAAA GACTATTGGAGAAAA ACTATTGGAGAAAAT CTATTGGAGAAAATA TATTGGAGAAAATAA ATTGGAGAAAATAAG TTGGAGAAAATAAGG TGGAGAAAATAAGGT GGAGAAAATAAGGTG GAGAAAATAAGGTGG AGAAAATAAGGTGGA GAAAATAAGGTGGAG AAAATAAGGTGGAGT AAATAAGGTGGAGTC AATAAGGTGGAGTCC ATAAGGTGGAGTCCT TAAGGTGGAGTCCTA AAGGTGGAGTCCTAC AGGTGGAGTCCTACT GGTGGAGTCCTACTT GTGGAGTCCTACTTG TGGAGTCCTACTTGT GGAGTCCTACTTGTT GAGTCCTACTTGTTT AGTCCTACTTGTTTA GTCCTACTTGTTTAA TCCTACTTGTTTAAA CCTACTTGTTTAAAA CTACTTGTTTAAAAA TACTTGTTTAAAAAA ACTTGTTTAAAAAAT CTTGTTTAAAAAATA TTGTTTAAAAAATAT TGTTTAAAAAATATG GTTTAAAAAATATGT TTTAAAAAATATGTA TTAAAAAATATGTAT TAAAAAATATGTATC AAAAAATATGTATCT AAAAATATGTATCTA AAAATATGTATCTAA AATATGTATCTAAGA ATATGTATCTAAGAA TATGTATCTAAGAAT ATGTATCTAAGAATG TGTATCTAAGAATGT	GTATCTAAGAATGTT TATCTAAGAATGTTT ATCTAAGAATGTTCT TCTAAGAATGTTCTA CTAAGAATGTTCTAG TAAGAATGTTCTAGG AAGAATGTTCTAGGG AGAATGTTCTAGGGC GAATGTTCTAGGGCA AATGTTCTAGGGCAC ATGTTCTAGGGCACT TGTTCTAGGGCACTC GTTCTAGGGCACTCT TTCTAGGGCACTCTG TCTAGGGCACTCTGG CTAGGGCACTCTGGG TAGGGCACTCTGGGA AGGGCACTCTGGGAA GGGCACTCTGGGAAC GGCACTCTGGGAACC GCACTCTGGGAACCT CACTCTGGGAACCTA ACTCTGGGAACCTAT CTCTGGGAACCTATA TCTGGGAACCTATAA CTGGGAACCTATAAA TGGAACCTATAAAGG GGGAACCTATAAAGG GGAACCTATAAAGGC GAACCTATAAAGGCA AACCTATAAAGGCAG ACCTATAAAGGCAGG CCTATAAAGGCAGGT CTATAAAGGCAGGTA TATAAAGGCAGGTAT ATAAAGGCAGGTATT TAAAGGCAGGTATTT AAAGGCAGGTATTTT AAGGCAGGTATTTTC AGGCAGGTATTTTCG GGCAGGTATTTTCGG GCAGGTATTTTCGGG CAGGTATTTTCGGGCC AGGTATTTTCGGGCCC GGTATTTTCGGGCCCT GTATTTTCGGGCCCTC TATTTTCGGGCCCTCC ATTTTCGGGCCCTCCT TTTCGGGCCCTCCTC TTCGGGCCCTCCTCT TCGGGCCCTCCTCTT
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5 ACTGCAGAAAATAGT	CTGAGGATAAGCTCT	GTCTCCTTAGCACA
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ACAAC	TTTATTTTCATCTCT	TAGTAATATCAGAAC
CAAC	TTATTTTCATCTCTC	AGTAATATCAGAAC
35 AACTCAAGACGAAGC	TATTTTCATCTCTCA	GTAATATCAGAACAG
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50 GAGATTCA	TAATTCACACATATA	ACATAGCCCCAAATA
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10 CAGGGAGACTCTGCC	AGCTCTCCTTGAAAA	TTTTCTTTATTTTTT
AGGGAGACTCTGCCC	GCTCTCCTTGAAAAC	TTTCTTTATTTTTTT
GGGAGACTCTGCCCT	CTCTCCTTGAAAACA	TTCTTTATTTTTTTA
GGAGACTCTGCCCTG	TCTCCTTGAAAACAG	TCTTTATTTTTTTAA
GAGACTCTGCCCTGC	CTCCTTGAAAACAGA	CTTTATTTTTTTAAC
15 AGACTCTGCCCTGCT	TCCTTGAAAACAGAG	TTTATTTTTTTAACT
GACTCTGCCCTGCTG	CCTTGAAAACAGAGG	TTATTTTTTTAACTT
ACTCTGCCCTGCTGC	CTTGAAAACAGAGGG	TATTTTTTTAACTTT
CTCTGCCCTGCTGCA	TTGAAAACAGAGGGG	ATTTTTTTAACTTTT
TCTGCCCTGCTGCAG	TGAAAACAGAGGGGT	TTTTTTTAACTTTTT
20 CTGCCCTGCTGCAGA	GAAAACAGAGGGGTC	TTTTTTTAACTTTTTG
TGCCCTGCTGCAGAC	AAAACAGAGGGGTCT	TTTTTTAACTTTTTGG
GCCCTGCTGCAGACC	AAACAGAGGGGTCTC	TTTTAACTTTTTTGGG
CCCTGCTGCAGACCT	AACAGAGGGGTCTCA	TTTAACTTTTTTGGGG
CCTGCTGCAGACCTC	ACAGAGGGGTCTCAA	TTAACTTTTTTGGGGG
25 CTGCTGCAGACCTCG	CAGAGGGGTCTCAAG	TAACTTTTTGGGGGG
TGCTGCAGACCTCGG	AGAGGGGTCTCAAGA	AACTTTTTGGGGGGGA
GCTGCAGACCTCGGT	GAGGGGTCTCAAGAC	ACTTTTTTGGGGGGAA
CTGCAGACCTCGGTG	AGGGGTCTCAAGACA	CTTTTTTGGGGGGAAA
TGCAGACCTCGGTGT	GGGGTCTCAAGACAT	TTTTTGGGGGGGAAAA
30 GCAGACCTCGGTGTG	GGGTCTCAAGACATT	TTTTTGGGGGGGAAAAG
CAGACCTCGGTGTGG	GGTCTCAAGACATTCT	TTTGGGGGGGAAAAGT
AGACCTCGGTGTGGA	GTCTCAAGACATTCT	TTGGGGGGGAAAAGTA
GACCTCGGTGTGGAC	TCTCAAGACATTCTG	TGGGGGGGAAAAGTAT
ACCTCGGTGTGGACA	CTCAAGACATTCTGC	GGGGGGGAAAAGTATT
35 CCTCGGTGTGGACAC	TCAAGACATTCTGCC	GGGGGAAAAGTATTTT
CTCGGTGTGGACACA	CAAGACATTCTGCCT	GGGGAAAAGTATTTTT
TCGGTGTGGACACAC	AAGACATTCTGCCTA	GGGAAAAGTATTTTTT
CGGTGTGGACACACG	AGACATTCTGCCTAC	GGAAAAGTATTTTTTG
GGTGTGGACACACGC	GACATTCTGCCTACC	GAAAAGTATTTTTTGA
40 GTGTGGACACACGCT	ACATTCTGCCTACCT	AAAAGTATTTTTTGAG
TGTGGACACACGCTG	CATTCTGCCTACCTA	AAAGTATTTTTTGAGA
GTGGACACACGCTGC	ATTCTGCCTACCTAT	AAGTATTTTTTGAGAA
TGGACACACGCTGCA	TTCTGCCTACCTATT	AGTATTTTTTGAGAAG
GGACACACGCTGCAT	TCTGCCTACCTATTA	GTATTTTTTGAGAAGT
45 GACACACGCTGCATA	CTGCCTACCTATTAG	TATTTTTTGAGAAGTT
ACACACGCTGCATAG	TGCCTACCTATTAGC	ATTTTTTGAGAAGTTT
CACACGCTGCATAGA	GCCTACCTATTAGCT	TTTTTGAGAAGTTTG
ACACGCTGCATAGAG	CCTACCTATTAGCTT	TTTTTGAGAAGTTTGT
CACGCTGCATAGAGC	CTACCTATTAGCTTT	TTTGAGAAGTTTGTCT
50 ACGCTGCATAGAGCT	TACCTATTAGCTTTT	TTGAGAAGTTTGTCTT
CGCTGCATAGAGCTC	ACCTATTAGCTTTTC	



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GAGAAGTTTGTCTTG  
 AGAAGTTTGTCTTGC  
 GAAGTTTGTCTTGCA  
 AAGTTTGTCTTGCAA  
 5 AGTTTGTCTTGCAAT  
 GTTTGTCTTGCAATG  
 TTTGTCTTGCAATGT  
 TTGTCTTGCAATGTA  
 TGTCTTGCAATGTAT  
 10 GTCTTGCAATGTATT  
 TCTTGCAATGTATTT  
 CTTGCAATGTATTTA  
 TTGCAATGTATTTAT  
 TGCAATGTATTTATA  
 15 GCAATGTATTTATAA  
 CAATGTATTTATAAA  
 AATGTATTTATAAAT  
 ATGTATTTATAAATA  
 TGTATTTATAAATAG  
 20 GTATTTATAAATAGT  
 TATTTATAAATAGTA  
 ATTTATAAATAGTAA  
 TTTATAAATAGTAAA  
 TTATAAATAGTAAAT  
 25 TATAAATAGTAAATA  
 ATAAATAGTAAATAA  
 TAAATAGTAAATAAA  
 AAATAGTAAATAAAG  
 AATAGTAAATAAAGT  
 30 ATAGTAAATAAAGTT  
 TAGTAAATAAAGTTT  
 AGTAAATAAAGTTTT  
 GTAAATAAAGTTTTT  
 TAAATAAAGTTTTTA  
 35 AAATAAAGTTTTTAC  
 AATAAAGTTTTTACC  
 ATAAAGTTTTTACCA  
 TAAAGTTTTTACCAT  
 AAAGTTTTTACCATT  
 40

**EXAMPLE 8**

Antisense oligonucleotides to IGF-I may be selected from molecules capable of interacting with one or more of the following sense oligonucleotides:

45

TTTTTTTTTTTTTTG  
 TTTTTTTTTTTTTGA  
 TTTTTTTTTTTTTGAG

TTTTTTTTTTTTGAGA  
 TTTTTTTTTTTTGAGAA  
 TTTTTTTTTTTTGAGAAA

TTTTTTTTGAGAAAG  
 TTTTTTTTGAGAAAGG  
 TTTTTTTTGAGAAAGGG

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TTTTTGAGAAAGGGA	GGAGGAGGGTCCCCG	CTCTCGCTCTGGCCG
TTTTGAGAAAGGGAA	GAGGAGGGTCCCCGA	TCTCGCTCTGGCCGA
TTTGAGAAAGGGAAT	AGGAGGGTCCCCGAC	CTCGCTCTGGCCGAC
TTGAGAAAGGGAATT	GGAGGGTCCCCGACC	TCGCTCTGGCCGACG
5 TGAGAAAGGGAATTT	GAGGGTCCCCGACCT	CGCTCTGGCCGACGA
GAGAAAGGGAATTTT	AGGGTCCCCGACCTC	GCTCTGGCCGACGAG
AGAAAGGGAATTTCA	GGGTCCCCGACCTCG	CTCTGGCCGACGAGT
GAAAGGGAATTTTCAT	GGTCCCCGACCTCGC	TCTGGCCGACGAGTG
AAAGGGAATTTTCATC	GTCCCCGACCTCGCT	CTGGCCGACGAGTGG
10 AAGGGAATTTTCATCC	TCCCCGACCTCGCTG	TGGCCGACGAGTGGA
AGGGAATTTTCATCCC	CCCCGACCTCGCTGT	GGCCGACGAGTGAGG
GGGAATTTTCATCCCA	CCCGACCTCGCTGTG	GCCGACGAGTGAGAA
GGAATTTTCATCCCAA	CCGACCTCGCTGTGG	CGACGAGTGAGAAA
GAATTTTCATCCCAAA	CGACCTCGCTGTGGG	GACGAGTGAGAAAT
15 AATTTTCATCCCAAAT	GACCTCGCTGTGGGG	ACGAGTGAGAAATC
ATTTTCATCCCAAATA	ACCTCGCTGTGGGGG	CGAGTGAGAAATCT
TTTCATCCCAAATAAA	CCTCGCTGTGGGGGC	GAGTGAGAAATCTG
TTCATCCCAAATAAAA	CTCGCTGTGGGGGCT	AGTGAGAAATCTGC
20 CATCCCAAATAAAAAG	CGCTGTGGGGGCTCC	GTGGAGAAATCTGCG
ATCCCAAATAAAAAGG	GCTGTGGGGGCTCCT	TGGAGAAATCTGCGG
TCCCAAATAAAAAGGA	CTGTGGGGGCTCCTG	GGAGAAATCTGCGGG
CCCAAATAAAAAGGAA	TGTGGGGGCTCCTGT	GAGAAATCTGCGGGC
CCAAATAAAAAGGAAT	GTGGGGGCTCCTGTT	AGAAATCTGCGGGCC
25 CAAATAAAAAGGAATG	TGGGGGCTCCTGTTT	GAAATCTGCGGGCCA
AAATAAAAAGGAATGA	GGGGGCTCCTGTTTC	AAATCTGCGGGCCAG
AATAAAAAGGAATGAA	GGGGCTCCTGTTTCT	AATCTGCGGGCCAGG
ATAAAAAGGAATGAAG	GGGCTCCTGTTTCTC	ATCTGCGGGCCAGGC
TAAAAGGAATGAAGT	GGCTCCTGTTTCTCT	TCTGCGGGCCAGGCA
30 AAAAGGAATGAAGTC	GCTCCTGTTTCTCTC	CTGCGGGCCAGGCAT
AAAGGAATGAAGTCT	CTCCTGTTTCTCTCC	TGCGGGCCAGGCATC
AAGGAATGAAGTCTG	TCCTGTTTCTCTCCG	GCGGGCCAGGCATCG
AGGAATGAAGTCTGG	CCTGTTTCTCTCCGC	CGGGCCAGGCATCGA
GGAATGAAGTCTGGC	CTGTTTCTCTCCGCC	GGGCCAGGCATCGAC
35 GAATGAAGTCTGGCT	TGTTTCTCTCCGCCG	GGCCAGGCATCGACA
AATGAAGTCTGGCTC	GTTTCTCTCCGCCGC	GCCAGGCATCGACAT
ATGAAGTCTGGCTCC	TTTCTCTCCGCCGCG	CCAGGCATCGACATC
TGAAGTCTGGCTCCG	TTCTCTCCGCCGCGC	CAGGCATCGACATCC
GAAGTCTGGCTCCGG	TCTCTCCGCCGCGCT	AGGCATCGACATCCG
40 AAGTCTGGCTCCGGA	CTCTCCGCCGCGCTC	GGCATCGACATCCGC
AGTCTGGCTCCGGAG	TCTCCGCCGCGCTCT	GCATCGACATCCGCA
GTCTGGCTCCGGAGG	CTCCGCCGCGCTCTC	CATCGACATCCGCAA
TCTGGCTCCGGAGGA	TCCGCCGCGCTCTCG	ATCGACATCCGCAAC
CTGGCTCCGGAGGAG	CCGCCGCGCTCTCGC	TCGACATCCGCAACG
45 TGGCTCCGGAGGAGG	CGCCGCGCTCTCGCT	CGACATCCGCAACGA
GGCTCCGGAGGAGGG	GCCGCGCTCTCGCTC	GACATCCGCAACGAC
GCTCCGGAGGAGGGT	CCGCGCTCTCGCTCT	ACATCCGCAACGACT
CTCCGGAGGAGGGTC	CGCGCTCTCGCTCTG	CATCCGCAACGACTA
TCCGGAGGAGGGTCC	GCGCTCTCGCTCTGG	ATCCGCAACGACTAT
50 CCGGAGGAGGGTCCC	CGCTCTCGCTCTGGC	TCCGCAACGACTATC
CGGAGGAGGGTCCCC	GCTCTCGCTCTGGCC	CCGCAACGACTATCA

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	CGCAACGACTATCAG	GGCTACCTCCACATC	CGCTTCCCCAAGCTC
	GCAACGACTATCAGC	GCTACCTCCACATCC	GCTTCCCCAAGCTCA
	CAACGACTATCAGCA	CTACCTCCACATCCT	CTTCCCCAAGCTCAC
	AACGACTATCAGCAG	TACCTCCACATCCTG	TTCCCCAAGCTCACG
5	ACGACTATCAGCAGC	ACCTCCACATCCTGC	TCCCCAAGCTCACGG
	CGACTATCAGCAGCT	CCTCCACATCCTGCT	CCCCAAGCTCACGGT
	GACTATCAGCAGCTG	CTCCACATCCTGCTC	CCCAAGCTCACGGTC
	ACTATCAGCAGCTGA	TCCACATCCTGCTCA	CCAAGCTCACGGTCA
	CTATCAGCAGCTGAA	CCACATCCTGCTCAT	CAAGCTCACGGTCAT
10	TATCAGCAGCTGAAG	CACATCCTGCTCATC	AAGCTCACGGTCATT
	ATCAGCAGCTGAAGC	ACATCCTGCTCATCT	AGCTCACGGTCATTA
	TCAGCAGCTGAAGCG	CATCCTGCTCATCTC	GCTCACGGTCATTAC
	CAGCAGCTGAAGCGC	ATCCTGCTCATCTCC	CTCACGGTCATTACC
	AGCAGCTGAAGCGCC	TCCTGCTCATCTCCA	TCACGGTCATTACCG
15	GCAGCTGAAGCGCCT	CCTGCTCATCTCCAA	CACGGTCATTACCGA
	CAGCTGAAGCGCCTG	CTGCTCATCTCCAAG	ACGGTCATTACCGAG
	AGCTGAAGCGCCTGG	TGCTCATCTCCAAGG	CGGTCATTACCGAGT
	GCTGAAGCGCCTGGA	GCTCATCTCCAAGGC	GGTCATTACCGAGTA
	CTGAAGCGCCTGGAG	CTCATCTCCAAGGCC	GTCATTACCGAGTAC
20	TGAAGCGCCTGGAGA	TCATCTCCAAGGCCG	TCATTACCGAGTACT
	GAAGCGCCTGGAGAA	CATCTCCAAGGCCGA	CATTACCGAGTACTT
	AAGCGCCTGGAGAAC	ATCTCCAAGGCCGAG	ATTACCGAGTACTTG
	AGCGCCTGGAGAACT	TCTCCAAGGCCGAGG	TTACCGAGTACTTGC
	GCGCCTGGAGAACTG	CTCCAAGGCCGAGGA	TACCGAGTACTTGCT
25	CGCCTGGAGAACTGC	TCCAAGGCCGAGGAC	ACCGAGTACTTGCTG
	GCCTGGAGAACTGCA	CCAAGGCCGAGGACT	CCGAGTACTTGCTGC
	CCTGGAGAACTGCAC	CAAGGCCGAGGACTA	CGAGTACTTGCTGCT
	CTGGAGAACTGCACG	AAGGCCGAGGACTAC	GAGTACTTGCTGCTG
	TGGAGAACTGCACGG	AGGCCGAGGACTACC	AGTACTTGCTGCTGT
30	GGAGAACTGCACGGT	GGCCGAGGACTACCG	GTACTTGCTGCTGTT
	GAGAACTGCACGGTG	GCCGAGGACTACCGC	TACTTGCTGCTGTTT
	AGAACTGCACGGTGA	CCGAGGACTACCGCA	ACTTGCTGCTGTTCC
	GAACTGCACGGTGAT	CGAGGACTACCGCAG	CTTGCTGCTGTTCCG
	AACTGCACGGTGATC	GAGGACTACCGCAGC	TTGCTGCTGTTCCGA
35	ACTGCACGGTGATCG	AGGACTACCGCAGCT	TGCTGCTGTTCCGAG
	CTGCACGGTGATCGA	GGACTACCGCAGCTA	GCTGCTGTTCCGAGT
	TGCACGGTGATCGAG	GACTACCGCAGCTAC	CTGCTGTTCCGAGTG
	GCACGGTGATCGAGG	ACTACCGCAGCTACC	TGCTGTTCCGAGTGG
	CACGGTGATCGAGGG	CTACCGCAGCTACCG	GCTGTTCCGAGTGGC
40	ACGGTGATCGAGGGC	TACCGCAGCTACCGC	CTGTTCCGAGTGGCT
	CGGTGATCGAGGGCT	ACCGCAGCTACCGCT	TGTTCCGAGTGGCTG
	GGTGATCGAGGGCTA	CCGCAGCTACCGCTT	GTTCCGAGTGGCTGG
	GTGATCGAGGGCTAC	CGCAGCTACCGCTTC	TTCCGAGTGGCTGGC
	TGATCGAGGGCTACC	GCAGCTACCGCTTCC	TCCGAGTGGCTGGCC
45	GATCGAGGGCTACCT	CAGCTACCGCTTCCC	CCGAGTGGCTGGCCT
	ATCGAGGGCTACCTC	AGCTACCGCTTCCCC	CGAGTGGCTGGCCTC
	TCGAGGGCTACCTCC	GCTACCGCTTCCCCA	GAGTGGCTGGCCTCG
	CGAGGGCTACCTCCA	CTACCGCTTCCCCAA	AGTGGCTGGCCTCGA
	GAGGGCTACCTCCAC	TACCGCTTCCCCAAG	GTGGCTGGCCTCGAG
50	AGGGCTACCTCCACA	ACCGCTTCCCCAAGC	TGGCTGGCCTCGAGA
	GGGCTACCTCCACAT	CCGCTTCCCCAAGCT	GGCTGGCCTCGAGAG

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GCTGGCCTCGAGAGC	GGCTGGAAACTCTTC	CTCAAGGATATTGGG
CTGGCCTCGAGAGCC	GCTGGAAACTCTTCT	TCAAGGATATTGGGC
TGGCCTCGAGAGCCT	CTGGAAACTCTTCTA	CAAGGATATTGGGCT
GGCCTCGAGAGCCTC	TGGAAACTCTTCTAC	AAGGATATTGGGCTT
5 GCCTCGAGAGCCTCG	GGAAACTCTTCTACA	AGGATATTGGGCTTT
CCTCGAGAGCCTCGG	GAAACTCTTCTACAA	GGATATTGGGCTTTA
CTCGAGAGCCTCGGA	AAACTCTTCTACAAC	GATATTGGGCTTTAC
TCGAGAGCCTCGGAG	AACTCTTCTACAAC	ATATTGGGCTTTACA
CGAGAGCCTCGGAGA	ACTCTTCTACAAC	TATTGGGCTTTACAA
10 GAGAGCCTCGGAGAC	CTCTTCTACAAC	ATTGGGCTTTACAAC
AGAGCCTCGGAGACC	TCTTCTACAAC	TTGGGCTTTACAACC
GAGCCTCGGAGACCT	CTTCTACAAC	TGGGCTTTACAACCT
AGCCTCGGAGACCTC	TTCTACAAC	GGGCTTTACAACCTG
GCCTCGGAGACCTCT	TCTACAAC	GGCTTTACAACCTGA
15 CCTCGGAGACCTCTT	CTACAAC	GCTTTACAACCTGAG
CTCGGAGACCTCTTC	TACAAC	CTTTACAACCTGAGG
TCGGAGACCTCTTCC	ACAAC	TTTACAACCTGAGGA
CGGAGACCTCTTCCC	CAAC	TTACAACCTGAGGAA
GGAGACCTCTTCCCC	AACT	TACAACCTGAGGAAC
20 GAGACCTCTTCCCCA	ACT	ACAACCTGAGGAACA
AGACCTCTTCCCCAA	CTAC	CAACCTGAGGAACAT
GACCTCTTCCCCAAC	TACG	AACCTGAGGAACATT
ACCTCTTCCCCAACC	ACG	ACCTGAGGAACATTA
CCTCTTCCCCAACCT	CGC	CCTGAGGAACATTAC
25 CTCTTCCCCAACCTC	GCC	CTGAGGAACATTACT
TCTTCCCCAACCTCA	CTT	TGAGGAACATTACTC
CTTCCCCAACCTCAC	CCT	GAGGAACATTACTCG
TTCCCCAACCTCACG	CTG	AGGAACATTACTCGG
TCCCCAACCTCACGG	TGG	GGAACATTACTCGGG
30 CCCCCAACCTCACGGT	GGT	GAACATTACTCGGGG
CCCAACCTCACGGTC	GTC	AACATTACTCGGGGG
CCAACCTCACGGTCA	TCAT	ACATTACTCGGGGGG
CAACCTCACGGTCAT	CAT	CATTACTCGGGGGGC
AACCTCACGGTCATC	ATCT	ATTACTCGGGGGGCC
35 ACCTCACGGTCATCC	TCTT	TTACTCGGGGGGCCA
CCTCACGGTCATCCG	CTTC	TACTCGGGGGGCCAT
CTCACGGTCATCCGC	TTG	ACTCGGGGGGCCATC
TCACGGTCATCCGCG	TCG	CTCGGGGGGCCATCA
CACGGTCATCCGCGG	CGA	TCGGGGGGGCCATCAG
40 ACGGTCATCCGCGGC	GAG	CGGGGGGCCATCAGG
CGGTCATCCGCGGCT	AGAT	GGGGGGGCCATCAGGA
GGTCATCCGCGGCTG	GATG	GGGGGGCCATCAGGAT
GTCATCCGCGGCTGG	GATG	GGGGCCATCAGGATT
TCATCCGCGGCTGGA	ATG	GGGCCATCAGGATTG
45 CATCCGCGGCTGGAA	TGAC	GGCCATCAGGATTGA
ATCCGCGGCTGGAAA	CAAT	GCCATCAGGATTGAG
TCCGCGGCTGGAAAC	CTCA	CCATCAGGATTGAGA
CCGCGGCTGGAAACT	CAAG	CATCAGGATTGAGAA
CGCGGCTGGAAACTC	GATA	ATCAGGATTGAGAAA
50 GCGGCTGGAAACTCT	ATAT	TCAGGATTGAGAAAA
CGGCTGGAAACTCTT	TATT	CAGGATTGAGAAAAA

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AGGATTGAGAAAAAT	CTGATCCTGGATGCG	AAGGAATGTGGGGAC
GGATTGAGAAAAATG	TGATCCTGGATGCGG	AGGAATGTGGGGACC
GATTGAGAAAAATGC	GATCCTGGATGCGGT	GGAATGTGGGGACCT
ATTGAGAAAAATGCT	ATCCTGGATGCGGTG	GAATGTGGGGACCTG
5 TTGAGAAAAATGCTG	TCCTGGATGCGGTGT	AATGTGGGGACCTGT
TGAGAAAAATGCTGA	CCTGGATGCGGTGTC	ATGTGGGGACCTGTG
GAGAAAAATGCTGAC	CTGGATGCGGTGTCC	TGTGGGGACCTGTGT
AGAAAAATGCTGACC	TGGATGCGGTGTCCA	GTGGGGACCTGTGTC
GAAAAATGCTGACCT	GGATGCGGTGTCCAA	TGGGGACCTGTGTCC
10 AAAAATGCTGACCTC	GATGCGGTGTCCAAT	GGGGACCTGTGTCCA
AAAATGCTGACCTCT	ATGCGGTGTCCAATA	GGGACCTGTGTCCAG
AAATGCTGACCTCTG	TGCGGTGTCCAATAA	GGACCTGTGTCCAGG
AATGCTGACCTCTGT	GCGGTGTCCAATAAC	GACCTGTGTCCAGGG
ATGCTGACCTCTGTT	CGGTGTCCAATAACT	ACCTGTGTCCAGGGA
15 TGCTGACCTCTGTTA	GGTGTCCAATAACTA	CCTGTGTCCAGGGAC
GCTGACCTCTGTTAC	GTGTCCAATAACTAC	CTGTGTCCAGGGACC
CTGACCTCTGTTACC	TGTCCAATAACTACA	TGTGTCCAGGGACCA
TGACCTCTGTTACCT	GTCCAATAACTACAT	GTGTCCAGGGACCAT
GACCTCTGTTACCTC	TCCAATAACTACATT	TGTCCAGGGACCATG
20 ACCTCTGTTACCTCT	CCAATAACTACATTG	GTCCAGGGACCATGG
CCTCTGTTACCTCTC	CAATAACTACATTGT	TCCAGGGACCATGGA
CTCTGTTACCTCTCC	AATAACTACATTGTG	CCAGGGACCATGGAG
TCTGTTACCTCTCCA	ATAACTACATTGTGG	CAGGGACCATGGAGG
CTGTTACCTCTCCAC	TAATACTACATTGTGGG	AGGGACCATGGAGGA
25 TGTTACCTCTCCACT	AACTACATTGTGGGG	GGGACCATGGAGGAG
GTTACCTCTCCACTG	ACTACATTGTGGGGA	GGACCATGGAGGAGA
TTACCTCTCCACTGT	CTACATTGTGGGGAA	GACCATGGAGGAGAA
TACCTCTCCACTGTG	TACATTGTGGGGAAT	ACCATGGAGGAGAAG
ACCTCTCCACTGTGG	ACATTGTGGGGAATA	CCATGGAGGAGAAGC
30 CCTCTCCACTGTGGA	CATTGTGGGGAATAA	CATGGAGGAGAAGCC
CTCTCCACTGTGGAC	ATTGTGGGGAATAAG	ATGGAGGAGAAGCCG
TCTCCACTGTGGACT	TTGTGGGGAATAAGC	TGGAGGAGAAGCCGA
CTCCACTGTGGACTG	TGTGGGGAATAAGCC	GGAGGAGAAGCCGAT
TCCACTGTGGACTGG	GTGGGGAATAAGCCC	GAGGAGAAGCCGATG
35 CCACTGTGGACTGGT	TGGGGAATAAGCCCC	AGGAGAAGCCGATGT
CACTGTGGACTGGTC	GGGGAATAAGCCCCC	GGAGAAGCCGATGTG
ACTGTGGACTGGTCC	GGGAATAAGCCCCCA	GAGAAGCCGATGTGT
CTGTGGACTGGTCCC	GGAATAAGCCCCCAA	AGAAGCCGATGTGTG
TGTGGACTGGTCCCT	GAATAAGCCCCCAAA	GAAGCCGATGTGTGA
40 GTGGACTGGTCCCTG	AATAAGCCCCCAAAG	AAGCCGATGTGTGAG
TGGACTGGTCCCTGA	ATAAGCCCCCAAAGG	AGCCGATGTGTGAGA
GGACTGGTCCCTGAT	TAAGCCCCCAAAGGA	GCCGATGTGTGAGAA
GACTGGTCCCTGATC	AAGCCCCCAAAGGAA	CCGATGTGTGAGAAG
ACTGGTCCCTGATCC	AGCCCCCAAAGGAAT	CGATGTGTGAGAAGA
45 CTGGTCCCTGATCCT	GCCCCCAAAGGAATG	GATGTGTGAGAAGAC
TGGTCCCTGATCCTG	CCCCCAAAGGAATGT	ATGTGTGAGAAGACC
GGTCCCTGATCCTGG	CCCCAAAGGAATGTG	TGTGTGAGAAGACCA
GTCCCTGATCCTGGA	CCCAAAGGAATGTGG	GTGTGAGAAGACCAC
TCCCTGATCCTGGAT	CCAAAGGAATGTGGG	TGTGAGAAGACCACC
50 CCCTGATCCTGGATG	CAAAGGAATGTGGGG	GTGAGAAGACCACCA
CCTGATCCTGGATGC	AAAGGAATGTGGGGA	TGAGAAGACCACCAT

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GAGAAGACCACCATC	CGCTGCCAGAAAATG	AACAATGAGTGCTGC
AGAAGACCACCATCA	GCTGCCAGAAAATGT	ACAATGAGTGCTGCC
GAAGACCACCATCAA	CTGCCAGAAAATGTG	CAATGAGTGCTGCCA
AAGACCACCATCAAC	TGCCAGAAAATGTGC	AATGAGTGCTGCCAC
5 AGACCACCATCAACA	GCCAGAAAATGTGCC	ATGAGTGCTGCCACC
GACCACCATCAACAA	CCAGAAAATGTGCCC	TGAGTGCTGCCACCC
ACCACCATCAACAAT	CAGAAAATGTGCCCA	GAGTGCTGCCACCCC
CCACCATCAACAATG	AGAAAATGTGCCCAA	AGTGCTGCCACCCCG
CACCATCAACAATGA	GAAAATGTGCCCAAG	GTGCTGCCACCCCGA
10 ACCATCAACAATGAG	AAAATGTGCCCAAGC	TGCTGCCACCCCGAG
CCATCAACAATGAGT	AAATGTGCCCAAGCA	GCTGCCACCCCGAGT
CATCAACAATGAGTA	AATGTGCCCAAGCAC	CTGCCACCCCGAGTG
ATCAACAATGAGTAC	ATGTGCCCAAGCACG	TGCCACCCCGAGTGC
TCAACAATGAGTACA	TGTGCCCAAGCACGT	GCCACCCCGAGTGCC
15 CAACAATGAGTACAA	GTGCCCAAGCACGTG	CCACCCCGAGTGCTT
AACAATGAGTACAAC	TGCCCAAGCACGTGT	CACCCCGAGTGCTTG
ACAATGAGTACAAC	GCCCAAGCACGTGTG	ACCCCGAGTGCTTGG
CAATGAGTACAAC	CCCAAGCACGTGTGG	CCCGAGTGCTTGGG
AATGAGTACAAC	CCAAGCACGTGTGGG	CCCGAGTGCTTGGGC
20 ATGAGTACAAC	CAAGCACGTGTGGGA	CCGAGTGCTTGGGCA
TGAGTACAAC	AAGCACGTGTGGGA	CGAGTGCTTGGGCAG
GAGTACAAC	AGCACGTGTGGGAAG	GAGTGCTTGGGCAGC
AGTACAAC	GCACGTGTGGGAAGC	AGTGCTTGGGCAGCT
GTACAAC	CACGTGTGGGAAGCG	GTGCTTGGGCAGCTG
25 TACAAC	ACGTGTGGGAAGCGG	TGCTTGGGCAGCTGC
ACAAC	CGTGTGGGAAGCGGG	GCCTTGGGCAGCTGCA
CAAC	GTGTGGGAAGCGGGC	CCTTGGGCAGCTGCAG
AACTACCGCTGCTG	TGTGGGAAGCGGGCG	CTGGGCAGCTGCAGC
ACTACCGCTGCTGGA	GTGGGAAGCGGGCGT	TGGGCAGCTGCAGCG
30 CTACCGCTGCTGGAC	TGGGAAGCGGGCGTG	GGGCAGCTGCAGCGC
TACCGCTGCTGGACC	GGGAAGCGGGCGTGCA	GCAGCTGCAGCGCGC
ACCGCTGCTGGACCA	GAAGCGGGCGTGCA	CAGCTGCAGCGCGCC
CCGCTGCTGGACCAC	AAGCGGGCGTGCA	AGCTGCAGCGCGCCT
CGCTGCTGGACCACA	AGCGGGCGTGCA	GCTGCAGCGCGCCTG
35 GCTGCTGGACCACAA	GCGGGCGTGCA	CTGCAGCGCGCCTGA
CTGCTGGACCACAAA	CGGGCGTGCA	TGCAGCGCGCCTGAC
TGCTGGACCACAAAC	GGGCGTGCA	GCAGCGCGCCTGACA
GCTGGACCACAAACC	GGCGTGCA	CAGCGCGCCTGACAA
CTGGACCACAAACCG	GCGTGCA	AGCGCGCCTGACAAC
40 TGGACCACAAACCGC	CGTGCA	GCGCGCCTGACAACG
GGACCACAAACCGCT	GTGCA	CGCGCCTGACAACGA
GACCACAAACCGCTG	TGCA	GCGCCTGACAACGAC
ACCACAAACCGCTGC	GCAC	CGCCTGACAACGACA
CCACAAACCGCTGCC	CACG	GCCTGACAACGACAC
45 CACAAACCGCTGCCA	ACCG	CCTGACAACGACACG
ACAAACCGCTGCCAG	CCG	CTGACAACGACACGG
CAAACCGCTGCCAGA	CG	TGACAACGACACGGC
AAACCGCTGCCAGAA	G	GACAACGACACGGCC
AACCGCTGCCAGAAA	GA	ACAACGACACGGCCT
50 ACCGCTGCCAGAAAA	GAACAATGAGTGCT	CAACGACACGGCCTG
CCGCTGCCAGAAAAT	GAACAATGAGTGCTG	

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AACGACACGGCCTGT	GTGCCTGCCTGCCCCG	GACCGTGA CTTCTG C
ACGACACGGCCTGTG	TGCTTGCCTGCCCCG	ACCGTGA CTTCTG C
CGACACGGCCTGTGT	GCCTGCCTGCCCCG	CCGTGA CTTCTG C
GACACGGCCTGTGTG	CCTGCCTGCCCCG	CGTGA CTTCTG C
5 ACACGGCCTGTGTAG	CTGCCTGCCCCG	GTGA CTTCTG C
CACGGCCTGTGTAGC	TGCCTGCCCCG	TGA CTTCTG C
ACGGCCTGTGTAGCT	GCCTGCCCCG	GAC CTTCTG C
CGGCCTGTGTAGCTT	CCTGCCCCG	ACT CTTCTG C
GGCCTGTGTAGCTTG	CTGCCCCG	CTT CTTCTG C
10 GCCTGTGTAGCTTGC	TGCCCCG	TT CTTCTG C
CCTGTGTAGCTTGCC	GCCCCG	TCTG CTTCTG C
CTGTGTAGCTTGCCG	CCCGCC	CTG CTTCTG C
TGTGTAGCTTGCCGC	CCGCC	TG CTTCTG C
GTGTAGCTTGCCGCC	CGCC	G CTTCTG C
15 TGTAGCTTGCCGCCA	GCC	CG CTTCTG C
GTAGCTTGCCGCCAC	CC	G CTTCTG C
TAGCTTGCCGCCACT	CA	CC
AGCTTGCCGCCACTA	CA	CA
GCTTGCCGCCACTAC	CA	CA
20 CTTGCCGCCACTACT	CA	CA
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TGCCGCCACTACTAC	CA	CA
GCCGCCACTACTACT	CA	CA
CCGCCACTACTACTA	CA	CA
25 CGCCACTACTACTAT	CA	CA
GCCACTACTACTATG	CA	CA
CCACTACTACTATGC	CA	CA
CACTACTACTATGCC	CA	CA
ACTACTACTATGCCG	CA	CA
30 CTACTACTATGCCGG	CA	CA
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CTACTATGCCGGTGT	CA	CA
TACTATGCCGGTGTG	CA	CA
35 ACTATGCCGGTGTCT	CA	CA
CTATGCCGGTGTCTG	CA	CA
TATGCCGGTGTCTGT	CA	CA
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TGCCGGTGTCTGTGT	CA	CA
40 GCCGGTGTCTGTGTG	CA	CA
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45 TGTCTGTGTGCCTGC	CA	CA
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TGTGTGCCTGCCTGC	CA	CA
50 GTGTGCCTGCCTGCC	CA	CA
TGTGCCTGCCTGCCC	CA	CA

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GGGTTTGTGATCCAC	ATCCGCAACGGCAGC	CCGAAGGTCTGTGAG
GGTTTGTGATCCACG	TCCGCAACGGCAGCC	CGAAGGTCTGTGAGG
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5 TTTGTGATCCACGACG	GCAACGGCAGCCAGA	AGGTCTGTGAGGAAG
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10 ATCCACGACGGCGAG	GGCAGCCAGAGCATG	TGTGAGGAAGAAAAAG
TCCACGACGGCGAGT	GCAGCCAGAGCATGT	GTGAGGAAGAAAAAGA
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15 CGACGGCGAGTGAT	CCAGAGCATGTACTG	GGAAGAAAAAGAAAAAC
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25 TGCATGCAGGAGTGC	TACTGCATCCCTTGT	AAAACAAAGACCATT
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30 GCAGGAGTGCCCC	CATCCCTTGTGAAGG	AAAGACCATTGATTCT
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35 AGTGCCCC	TTGTGAAGGTCTTG	CATTGATTCTGTTAC
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TGCCCC	GTGAAGGTCTTGCC	TTGATTCTGTTACTT
GCCCC	TGAAGGTCTTGCCC	TGATTCTGTTACTTCT
CCCC	GAAGGTCTTGCCCG	GATTCTGTTACTTCTG
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CCCC	TGCCCGAAGGTCTGT	ACTTCTGCTCAGATGC
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CCCC	CCCGAAGGTCTGTGA	TTCTGCTCAGATGCT



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TCTGCTCAGATGCTC	AACATCCGACGGGGG	CTCATCGAGGTGGTG
CTGCTCAGATGCTCC	ACATCCGACGGGGGA	TCATCGAGGTGGTGA
TGCTCAGATGCTCCA	CATCCGACGGGGGAA	CATCGAGGTGGTGAC
GCTCAGATGCTCCAA	ATCCGACGGGGGAAT	ATCGAGGTGGTGACG
5 CTCAGATGCTCCAAG	TCCGACGGGGGAATA	TCGAGGTGGTGACGG
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45 GCTCATTAACATCCG	ATGGGGCTCATCGAG	TGCCTTGGTCTCCTT
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CATTAACATCCGACG	GGGCTCATCGAGGTG	CTTGGTCTCCTTGTG
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50 TTAACATCCGACGGG	GCTCATCGAGGTGGT	TGGTCTCCTTGTCCCT
TAACATCCGACGGGG		GGTCTCCTTGTCCCT

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GTCTCCTTGTCTTC	CTAGAAGGGAATTAC	CTGTGGGACTGGGAC
TCTCCTTGTCTTCC	TAGAAGGGAATTACT	TGTGGGACTGGGACC
CTCCTTGTCTTCCT	AGAAGGGAATTACTC	GTGGGACTGGGACCA
TCCTTGTCTTCCTA	GAAGGGAATTACTCC	TGGGACTGGGACCAC
5 CCTTGTCTTCCTAA	AAGGGAATTACTCCT	GGGACTGGGACCACC
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10 TCCTTCCTAAAAAAC	AATTACTCCTTCTAC	TGGGACCACCGCAAC
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35 TCCTAGGAGAGGAGC	ACCAGAACTTGCA	AAGCAGGGAAAATGT
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45 GGAGCAGCTAGAAAG	GCAGCA	AATGTACTTTGCTTT
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50 AGCTAGAAAGGGAATT	AACTGTGGGACTGGG	ACTTTGCTTTCAATC
GCTAGAAAGGGAATTA	ACTGTGGGACTGGGA	CTTTGCTTTCAATCC

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TTTGCTTTCAATCCC	GTGACGGGGACTAAA	AACGGGGAGAGAGCC
TTGCTTTCAATCCCA	TGACGGGGACTAAAG	ACGGGGAGAGAGCCT
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5 CTTTCAATCCCAAAT	CGGGGACTAAAGGGC	GGGAGAGAGCCTCCT
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CAATCCCAAATTATG	GACTAAAGGGCGCCA	GAGAGCCTCCTGTGA
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CCAAATTATGTGTTT	AAGGGCGCCAAAGCA	CCTCCTGTGAAAGTG
15 CAAATTATGTGTTTC	AGGGCGCCAAAGCAA	CTCCTGTGAAAGTGA
AAATTATGTGTTTCC	GGGCGCCAAAGCAAA	TCCTGTGAAAGTGAC
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TGTTTCCGAAATTTA	AAGCAAAGGGGACAT	AAGTGACGTCTTGCA
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30 CGAAATTTACCGCAT	AGGGGACATAAACAC	CGTCTTGCA
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AATTTACCGCATGGA	GGACATAAACACCAG	CCTTGCA
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35 TTTACCGCATGGAGG	ACATAAACACCAGGA	TGCA
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50 AAGTGACGGGGACTA	ACAACGGGGAGAGAG	CCACC
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 CACGTCGAAGAATCG  
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 5 CGTCGAAGAATCGCA  
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 25 ATAACCTGGCACCGG  
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 40 TACCGGCCCCCTGAC  
 ACCGGCCCCCTGACT  
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 50 CTGACTACAGGGATC  
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 CTACAGGGATCTCAT  
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 CAGGGATCTCATCAG  
 AGGGATCTCATCAGC  
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 CATCAGCTTCACCGT  
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 AGCTGGAACATGGTG  
 GCTGGAACATGGTGG  
 CTGGAACATGGTGG  
 TGGAACATGGTGGAC  
 GGAACATGGTGGACG  
 GAACATGGTGGACGT

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ACATGGTGGACGTGG	TACTACATGGGCTGA	TGACCCTCACCATGG
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15 GGACCTCCCGCCCAA	GAAGCCCTGGACTCA	GGTGGAGAACGACCA
GACCTCCCGCCCAAC	AAGCCCTGGACTCAG	GTGGAGAACGACCAT
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CTCCCGCCCAACAAG	CCCTGGACTCAGTAC	GAGAACGACCATATC
20 TCCCGCCCAACAAGG	CCTGGACTCAGTACG	AGAACGACCATATCC
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25 CCCAACAAGGACGTG	ACTCAGTACGCCGTT	GACCATATCCGTGGG
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40 GAGCCCCGGCATCTTA	TACGTCAAGGCTGTG	GCCAAGAGTGAGATC
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50 TCTTACTACATGGGC	CTGTGACCCTCACCA	AGATCTTGTACATTG
CTTACTACATGGGCT	TGTGACCCTCACCAT	GATCTTGTACATTGC

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ATCTTGTACATTTCGC	CTTTCAGCATCGAAC	TCTCTGCCCCAACGGC
TCTTGTACATTTCGCA	TTTCAGCATCGAACT	CTCTGCCCCAACGGCA
CTTGTACATTTCGCAC	TTCAGCATCGAACTC	TCTGCCCCAACGGCAA
TTGTACATTTCGCACC	TCAGCATCGAACTCC	CTGCCCCAACGGCAAC
5 TGTACATTTCGCACCA	CAGCATCGAACTCCT	TGCCCCAACGGCAACC
GTACATTTCGCACCAA	AGCATCGAACTCCTC	GCCCCAACGGCAACCT
TACATTTCGCACCAAT	GCATCGAACTCCTCT	CCCAACGGCAACCTG
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CATTTCGCACCAATGC	ATCGAACTCCTCTTC	CAACGGCAACCTGAG
10 ATTCGCACCAATGCT	TCGAACTCCTCTTCT	AACGGCAACCTGAGT
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TCGCACCAATGCTTC	GAACTCCTCTTCTCA	CGGCAACCTGAGTTA
CGCACCAATGCTTCA	AACTCCTCTTCTCAG	GGCAACCTGAGTTAC
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15 CACCAATGCTTCAGT	CTCCTCTTCTCAGTT	CAACCTGAGTTACTA
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CAATGCTTCAGTTCC	CTCTTCTCAGTTAAT	CCTGAGTTACTACAT
AATGCTTCAGTTCCCT	TCTTCTCAGTTAATC	CTGAGTTACTACATT
20 ATGCTTCAGTTCCTT	CTTCTCAGTTAATCG	TGAGTTACTACATTG
TGCTTCAGTTCCTTC	TTCTCAGTTAATCGT	GAGTTACTACATTGT
GCTTCAGTTCCTTCC	TCTCAGTTAATCGTG	AGTTACTACATTGTG
CTTCAGTTCCTTCCA	CTCAGTTAATCGTGA	GTTACTACATTGTGC
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25 TCAGTTCCTTCCATT	CAGTTAATCGTGAAG	TACTACATTGTGCGC
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30 TCCTTCCATTCCCTT	AATCGTGAAGTGGA	CATTGTGCGCTGGCA
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35 CCATTCCCTTGGACG	TGAAGTGGAACCCCTC	TGCGCTGGCAGCGGC
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40 CCCTTGGACGTTCTT	TGGAACCCCTCCCTCT	TGGCAGCGGCAGCCT
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45 GGACGTTCTTTTCA	CCCTCCCTCTCTGCC	GCGGCAGCCTCAGGA
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50 TTCTTTTCA	CCTCTCTGCCCAACG	AGCCTCAGGACGGCT
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	CTCAGGACGGCTACC	CCATCAGGAAGTATG	ACCCCAAGACTGAGG
	TCAGGACGGCTACCT	CATCAGGAAGTATGC	CCCCAAGACTGAGGT
	CAGGACGGCTACCTT	ATCAGGAAGTATGCC	CCCAAGACTGAGGTG
5	AGGACGGCTACCTTT	TCAGGAAGTATGCCG	CCAAGACTGAGGTGT
	GGACGGCTACCTTTA	CAGGAAGTATGCCGA	CAAGACTGAGGTGTG
	GACGGCTACCTTTAC	AGGAAGTATGCCGAC	AAGACTGAGGTGTGT
	ACGGCTACCTTTACC	GGAAGTATGCCGACG	AGACTGAGGTGTGTG
	CGGCTACCTTTACCG	GAAGTATGCCGACGG	GACTGAGGTGTGTGG
10	GGCTACCTTTACCGG	AAGTATGCCGACGGC	ACTGAGGTGTGTGGT
	GCTACCTTTACCGGC	AGTATGCCGACGGCA	CTGAGGTGTGTGGTG
	CTACCTTTACCGGCA	GTATGCCGACGGCAC	TGAGGTGTGTGGTGG
	TACCTTTACCGGCAC	TATGCCGACGGCACC	GAGGTGTGTGGTGGG
	ACCTTTACCGGCACA	ATGCCGACGGCACCA	AGGTGTGTGGTGGGG
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	CTTTACCGGCACAAT	GCCGACGGCACCATC	GTGTGTGGTGGGGAG
	TTTACCGGCACAATT	CCGACGGCACCATCG	TGTGTGGTGGGGAGA
	TTACCGGCACAATTA	CGACGGCACCATCGA	GTGTGGTGGGGAGAA
	TACCGGCACAATTAC	GACGGCACCATCGAC	TGTGGTGGGGAGAAA
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	CCGGCACAATTACTG	CGGCACCATCGACAT	TGGTGGGGAGAAAGG
	CGGCACAATTACTGC	GGCACCATCGACATT	GGTGGGGAGAAAGGG
	GGCACAATTACTGCT	GCACCATCGACATTG	GTGGGGAGAAAGGGC
	GCACAATTACTGCTC	CACCATCGACATTGA	TGGGGAGAAAGGGCC
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	ACAATTACTGCTCCA	CCATCGACATTGAGG	GGGAGAAAGGGCCTT
	CAATTACTGCTCCAA	CATCGACATTGAGGA	GGAGAAAGGGCCTTG
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	ATTACTGCTCCAAAG	TCGACATTGAGGAGG	AGAAAGGGCCTTGCT
30	TTACTGCTCCAAAGA	CGACATTGAGGAGGT	GAAAGGGCCTTGCTG
	TACTGCTCCAAAGAC	GACATTGAGGAGGTC	AAAGGGCCTTGCTGC
	ACTGCTCCAAAGACA	ACATTGAGGAGGTCA	AAGGGCCTTGCTGCG
	CTGCTCCAAAGACAA	CATTGAGGAGGTCA	AGGGCCTTGCTGCGC
	TGCTCCAAAGACAAA	ATTGAGGAGGTCA	GGGCCTTGCTGCGCC
35	GCTCCAAAGACAAAA	TTGAGGAGGTCA	GGCCTTGCTGCGCCT
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	TCCAAAGACAAAATC	GAGGAGGTCA	CCTTGCTGCGCCTGC
	CCAAAGACAAAATCC	AGGAGGTCA	CTTGCTGCGCCTGCC
	CAAAGACAAAATCCC	GGAGGTCA	TTGCTGCGCCTGCC
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	AAGACAAAATCCCCA	AGGTCA	GCTGCGCCTGCCCCA
	AGACAAAATCCCCAT	GGTCA	CTGCGCCTGCCCCAA
	GACAAAATCCCCATC	GTC	TGCGCCTGCCCCAAA
	ACAAAATCCCCATCA	TC	GCGCCTGCCCCAAAA
45	CAAAATCCCCATCAG	CAC	CGCCTGCCCCAAAA
	AAAATCCCCATCAGG	AC	GCCTGCCCCAAAACT
	AAATCCCCATCAGGA	C	CCTGCCCCAAAACTG
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	ATCCCCATCAGGAAG	G	TGCCCCAAAACTGAA
50	TCCCCATCAGGAAGT	AGA	GCCCCAAAACTGAAG
	CCCCATCAGGAAGTA	GA	CCCCAAAACTGAAGC

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CCCCAACTGAAGCC	AAAGTCTTTGAGAAT	AGGAAGCGGAGAGAT
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5 AAACCTGAAGCCGAGA	TCTTTGAGAATTTCC	AGCGGAGAGATGTCA
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ACTGAAGCCGAGAAG	TTTGAGAATTTCCCTG	CGGAGAGATGTCATG
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10 GAAGCCGAGAAGCAG	GAGAATTTCCCTGCAC	AGAGATGTCATGCAA
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20 AGCAGGCCGAGAAGG	TGCACAAC	TGCAAGTGGCCAACA
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CAGGCCGAGAAGGAG	CACAAC	CAAGTGGCCAACACC
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GGCCGAGAAGGAGGA	CAAC	AGTGGCCAACACCAC
25 GCCGAGAAGGAGGAG	AACTCCATCTTCGTG	GTGGCCAACACCACC
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30 GAAGGAGGAGGCTGA	CATCTTCGTGCCCCAG	CAACACCACCATGTC
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45 ATACCGCAAAGTCTT	ACCTGAAAGGAAGCG	CAGCCGAAGCAGGAA
TACCGCAAAGTCTTT	CCTGAAAGGAAGCGG	AGCCGAAGCAGGAAC
ACCGCAAAGTCTTTG	CTGAAAGGAAGCGGA	GCCGAAGCAGGAACA
CCGCAAAGTCTTTGA	TGAAAGGAAGCGGAG	CCGAAGCAGGAACAC
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50 GCAAAGTCTTTGAGA	AAAGGAAGCGGAGAG	GAAGCAGGAACACCA
CAAAGTCTTTGAGAA	AAGGAAGCGGAGAGA	AAGCAGGAACACCAC



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AGCAGGAACACCACG	CTGGAGACAGAGTAC	ACTGTCATTTCTAAC
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AGGAACACCACGGCC	GAGACAGAGTACCCT	GTCATTTCTAACCTT
5 GGAACACCACGGCCG	AGACAGAGTACCCTT	TCATTTCTAACCTTC
GAACACCACGGCCGC	GACAGAGTACCCTTT	CATTTCTAACCTTCG
AACACCACGGCCGCA	ACAGAGTACCCTTTC	ATTTCTAACCTTCGG
ACACCACGGCCGCAG	CAGAGTACCCTTCT	TTTCTAACCTTCGGC
CACCACGGCCGCAGA	AGAGTACCCTTCTT	TTCTAACCTTCGGCC
10 ACCACGGCCGCAGAC	GAGTACCCTTCTTT	TCTAACCTTCGGCCT
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15 GGCCGCAGACACCTA	CCCTTCTTTGAGAG	CCTTCGGCCTTTCACA
GCCGCAGACACCTAC	CCTTCTTTGAGAGC	CTTCGGCCTTTCACA
CCGCAGACACCTACA	CTTCTTTGAGAGCA	TTTCGGCCTTTCACAT
CGCAGACACCTACAA	TTTCTTTGAGAGCAG	TCGGCCTTTCACATT
GCAGACACCTACAAC	TTCTTTGAGAGCAGA	CGGCCTTTCACATTG
20 CAGACACCTACAACA	TCCTTTGAGAGCAGAG	GGCCTTTCACATTGT
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GACACCTACAACATC	TTTGAGAGCAGAGTG	CCTTTCACATTGTAC
ACACCTACAACATCA	TTGAGAGCAGAGTGG	CTTTCACATTGTACC
CACCTACAACATCAC	TGAGAGCAGAGTGGA	TTTCACATTGTACCG
25 ACCTACAACATCACC	GAGAGCAGAGTGGAT	TTACATTGTACCGC
CCTACAACATCACCG	AGAGCAGAGTGGATA	TCACATTGTACCGCA
CTACAACATCACCGA	GAGCAGAGTGGATAA	CACATTGTACCGCAT
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30 CAACATCACCGACCC	CAGAGTGGATAACAA	ATTGTACCGCATCGA
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45 GGAAGAGCTGGAGAC	GGAGAGAACTGTCAT	TATCCACAGCTGCAA
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AGCTGCAACCACGAG	TTTGCAAGGACTATG	ACCTGGGAGCCAAGG
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5 GCAACCACGAGGCTG	CAAGGACTATGCCCC	GGGAGCCAAGGCCTG
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10 CACGAGGCTGAGAAG	ACTATGCCCCGAGAA	CCAAGGCCTGAAAAC
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35 GCGCCTCCAAC	ACATTCTTGGGCCAG	TAA
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45 CTT	GCCAGTGACCTGGGA	AG
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50 TCT	TGACCTGGGAGCCAA	AG
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 GATTTCAGGCCACATC  
 ATTCAGGCCACATCT  
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 CAGGCCACATCTCTCT  
 AGGCCACATCTCTCT  
 GGCCACATCTCTCTC

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GGAATGGGTCGTGGA	GATATGAAAAC	TGATCGTGGGAGGGT
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GTCGTGGACAGATCC	AAAC	GGGAGGGTTGGTGAT
25 TCGTGGACAGATCCT	AACT	GGAGGGTTGGTGATT
CGTGGACAGATCCTG	ACT	GAGGGTTGGTGATTAT
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TGGACAGATCCTGTG	TCAT	GGGTGGTGATTATG
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30 GACAGATCCTGTGTT	CAT	GTTGGTGATTATGCT
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CAGATCCTGTGTTCT	TCC	TGGTGATTATGCTGT
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GATCCTGTGTTCTTC	CAT	GTGATTATGCTGTAC
35 ATCCTGTGTTCTTCT	CTG	TGATTATGCTGTACG
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TGTGTTCTTCTATGT	GAT	TATGCTGTACGCTTT
40 GTGTTCTTCTATGTC	AT	ATGCTGTACGCTTTC
TGTTCTTCTATGTCC	TC	TGCTGTACGCTTTC
GTTCTTCTATGTCCA	CAT	GCTGTACGCTTTC
TTCTTCTATGTCCAG	AT	CTGTACGCTTTC
TCTTCTATGTCCAGG	TC	TGTACGCTTTC
45 CTTCTATGTCCAGGC	CG	GTACGCTTTC
TTCTATGTCCAGGCC	GCT	TACGCTTTC
TCTATGTCCAGGCCA	CT	ACGCTTTC
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TATGTCCAGGCCAAA	CTG	GTCTTTC
50 ATGTCCAGGCCAAAA	TG	TCTTTC
TGTCCAGGCCAAAAC	CCCC	CTTTC

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TTCCATAGAAAGAGA	TCTGTGAACCCGGAG	TGGGAGGTGGCTCGG
TCCATAGAAAGAGAA	CTGTGAACCCGGAGT	GGGAGGTGGCTCGGG
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5 ATAGAAAGAGAAATA	TGAACCCGGAGTACT	AGGTGGCTCGGGAGA
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10 AAGAGAAATAACAGC	CCGGAGTACTTCAGC	GCTCGGGAGAAGATC
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25 AGGCTGGGGAAATGGA	GCTGCTGATGTGTAC	ACCATGAGCCGGGAA
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50 CCTCTGTGAACCCGG	AGTGGGAGGTGGCTC	GGTCGTTTGGGATGG
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	TGGGATGGTCTATGA	AACCAGAGTGGCCAT	GATTGAGTTTCTCAA
	GGGATGGTCTATGAA	ACCAGAGTGGCCATT	ATTGAGTTTCTCAAC
	GGATGGTCTATGAAG	CCAGAGTGGCCATTA	TTGAGTTTCTCAACG
	GATGGTCTATGAAGG	CAGAGTGGCCATTAA	TGAGTTTCTCAACGA
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	AGTTGCCAAGGGTGT	AACAGTGAACGAGGC	AGCTTCTGTGATGAA
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	CCAAGGGTGTGGTGA	TGAACGAGGCCGCAA	CTGTGATGAAGGAGT
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	TGTGGTGAAAGATGA	GGCCGCAAGCATGCG	GAAGGAGTTCAATTG
	GTGGTGAAAGATGAA	GCCGCAAGCATGCGT	AAGGAGTTCAATTGT
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50	AACCTGAAACCAGAG	GTGAGAGGATTGAGT	GTCACCATGTGGTGC
	ACCTGAAACCAGAGT	TGAGAGGATTGAGTT	TCACCATGTGGTGC

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CACCATGTGGTGCGA	GTCATCATGGAAC TG	CTGAGGCCAGAAATG
ACCATGTGGTGCGAT	TCATCATGGAAC TG	TGAGGCCAGAAATGG
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CATGTGGTGCGATTG	ATCATGGAAC TG	AGGCCAGAAATGGAG
5 ATGTGGTGCGATTGC	TCATGGAAC TG	GGCCAGAAATGGAGA
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10 GTGCGATTGCTGGGT	GAAC TG	GAAATGGAGAATAAT
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15 ATTGCTGGGTGTGGT	GATGACACGGGGCGA	GGAGAATAATCCAGT
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25 GTGGTGTC	GGCGATCTCAAAAGT	CCAGTCCTAGCACCT
TGGTGTC	GCGATCTCAAAAGTT	CAGTCCTAGCACCTC
GGTGTC	CGATCTCAAAAGTTA	AGTCCTAGCACCTCC
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30 GTCCCAAGGCCAGCC	TCTCAAAAGTTATCT	CCTAGCACCTCCAAG
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ACTGGTCATCATGGA	GTCTCTGAGGCCAGA	GAGCAAGATGATTCA
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50 TGGTCATCATGGAAC	CTCTGAGGCCAGAAA	GCAAGATGATTGAGA
GGTCATCATGGAAC	TCTGAGGCCAGAAAT	CAAGATGATTGAGAT

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AAGATGATTCAGATG	GCCAATAAGTTCGTC	GAAGATTTTCACAGTC
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20 GAGAGATTGCAGACG	GAGACCTTGCTGCCC	TCGGAGATTTTGGTA
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25 ATTGACAGACGGCATG	CTTGCTGCCCCGAAT	GATTTTGGTATGACG
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35 GCATGGCATA	GGAATTGCATGGTAG	TGACGCGAGATATCT
CATGGCATA	GAATTGCATGGTAGC	GACGCGAGATATCTA
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CATAC	GCATGGTAGCCGAAG	GAGATATCTATGAGA
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CTCA	ATGGTAGCCGAAGAT	GATATCTATGAGACA
CTCA	TGGTAGCCGAAGATT	ATATCTATGAGACAG
45 CCTCA	GGTAGCCGAAGATTT	TATCTATGAGACAGA
CTCA	GTAGCCGAAGATTTT	ATCTATGAGACAGAC
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50 ACGCA	CCGAAGATTTTCA	ATGAGACAGACTATT
CGCA	CGAAGATTTTCA	TGAGACAGACTATTA



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5	GAGACAGACTATTAC AGACAGACTATTACC GACAGACTATTACCG ACAGACTATTACCGG CAGACTATTACCGGA AGACTATTACCGGAA GACTATTACCGGAAA ACTATTACCGGAAAG CTATTACCGGAAAGG	ATGTCTCCTGAGTCC TGTCTCCTGAGTCCC GTCTCCTGAGTCCCT TCTCCTGAGTCCCTC CTCCTGAGTCCCTCA TCCTGAGTCCCTCAA CCTGAGTCCCTCAAG CTGAGTCCCTCAAGG TGAGTCCCTCAAGGA GAGTCCCTCAAGGAT AGTCCCTCAAGGATG GTCCCTCAAGGATGG TCCCTCAAGGATGGA CCCTCAAGGATGGAG CCTCAAGGATGGAGT CTCAAGGATGGAGTC TCAAGGATGGAGTCT CAAGGATGGAGTCTT AAGGATGGAGTCTTC AGGATGGAGTCTTCA GGATGGAGTCTTCAC GATGGAGTCTTCACC ATGGAGTCTTCACCA TGGAGTCTTCACCAC GGAGTCTTCACCACT GAGTCTTCACCACTT AGTCTTCACCACTTA GTCTTCACCACTTAC TCTTCACCACTTACT CTTCACCACTTACTC TTCACCACTTACTCG TCACCACTTACTCGG CACCACTTACTCGGA ACCACTTACTCGGAC CCACTTACTCGGACG CACTTACTCGGACGT ACTTACTCGGACGTC CTTACTCGGACGTCT TTACTCGGACGTCTG TACTCGGACGTCTGG ACTCGGACGTCTGGT CTCGGACGTCTGGTC TCGGACGTCTGGTCC CGGACGTCTGGTCCT GGACGTCTGGTCCTT GACGTCTGGTCCTTC ACGTCTGGTCCTTCG CGTCTGGTCCTTCGG GTCTGGTCCTTCGGG TCTGGTCCTTCGGGG CTGGTCCTTCGGGGT	TGGTCCTTCGGGGTC GGTCCTTCGGGGTCG GTCCTTCGGGGTCGT TCCTTCGGGGTCGTCC CCTTCGGGGTCGTCC CTTCGGGGTCGTCTC TTCGGGGTCGTCTCTC TCGGGGTCGTCTCTCT CGGGGTCTCTCTCTG GGGGTCGTCTCTCTGG GGGTCTCTCTCTGGG GGTCTCTCTCTGGGA GTCGTCTCTCTGGGAG TCGTCTCTCTGGGAGA CGTCTCTCTGGGAGAT GTCCTCTCTGGGAGATC TCCTCTCTGGGAGATCG CCTCTCTGGGAGATCGC CTCTCTGGGAGATCGCC TCTCTGGGAGATCGCCA CTGGGAGATCGCCAC TGGGAGATCGCCACA GGGAGATCGCCACAC GGAGATCGCCACACT GAGATCGCCACACTG AGATCGCCACACTGG GATCGCCACACTGGC ATCGCCACACTGGCC TCGCCACACTGGCCG CGCCACACTGGCCGA GCCACACTGGCCGAG CCACACTGGCCGAGC CACACTGGCCGAGCA ACACTGGCCGAGCAG CACTGGCCGAGCAGC ACTGGCCGAGCAGCC CTGGCCGAGCAGCCC TGGCCGAGCAGCCCT GGCCGAGCAGCCCTA GCCGAGCAGCCCTAC CCGAGCAGCCCTACC CGAGCAGCCCTACCA GAGCAGCCCTACCAG AGCAGCCCTACCAGG GCAGCCCTACCAGGG CAGCCCTACCAGGGC AGCCCTACCAGGGCT GCCCTACCAGGGCTT CCCTACCAGGGCTTG CCTACCAGGGCTTGT CTACCAGGGCTTGTC
10	TATTACCGGAAAGGA ATTACCGGAAAGGAG TTACCGGAAAGGAGG TACCGGAAAGGAGGC ACCGGAAAGGAGGCA		
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50	GGATGTCTCCTGAGT GATGTCTCCTGAGTC		

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25 GTCCTTCGCTTCGTC	CCT	ATGAGGCCTTCCTTC
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45 GGGCGGCCTTCTGGA	GAAT	GATCATCAGCAGCAT
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50 GCCTTCTGGACAAGC	GAAT	TCAGCAGCATCAAAG
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	AGCATCAAAGAGGAG	AGCGAGGAGAACAAAG	AACATGGAGAGCGTC
5	GCATCAAAGAGGAGA	GCGAGGAGAACAAAGC	ACATGGAGAGCGTCC
	CATCAAAGAGGAGAT	CGAGGAGAACAAAGCT	CATGGAGAGCGTCCC
	ATCAAAGAGGAGATG	GAGGAGAACAAAGCTG	ATGGAGAGCGTCCCC
	TCAAAGAGGAGATGG	AGGAGAACAAAGCTGC	TGGAGAGCGTCCCCC
	CAAAGAGGAGATGGA	GGAGAACAAAGCTGCC	GGAGAGCGTCCCCCT
10	AAAGAGGAGATGGAG	GAGAACAAAGCTGCCC	GAGAGCGTCCCCCTG
	AAGAGGAGATGGAGC	AGAACAAGCTGCCCCG	AGAGCGTCCCCCTGG
	AGAGGAGATGGAGCC	GAACAAGCTGCCCCGA	GAGCGTCCCCCTGGA
	GAGGAGATGGAGCCT	AACAAGCTGCCCCGAG	AGCGTCCCCCTGGAC
	AGGAGATGGAGCCTG	ACAAGCTGCCCCGAGC	GCGTCCCCCTGGACC
15	GGAGATGGAGCCTGG	CAAGCTGCCCCGAGCC	CGTCCCCCTGGACCC
	GAGATGGAGCCTGGC	AAGCTGCCCCGAGCCG	GTCCCCCTGGACCCC
	AGATGGAGCCTGGCT	AGCTGCCCCGAGCCGG	TCCCCCTGGACCCCCT
	GATGGAGCCTGGCTT	GCTGCCCCGAGCCGGA	CCCCCTGGACCCCCTC
	ATGGAGCCTGGCTTC	CTGCCCCGAGCCGGAG	CCCCTGGACCCCCTCG
20	TGGAGCCTGGCTTCC	TGCCCCGAGCCGGAGG	CCCTGGACCCCCTCGG
	GGAGCCTGGCTTCCG	GCCCCGAGCCGGAGGA	CCTGGACCCCCTCGGC
	GAGCCTGGCTTCCGG	CCCGAGCCGGAGGAG	CTGGACCCCCTCGGCC
	AGCCTGGCTTCCGGG	CCGAGCCGGAGGAGC	TGGACCCCCTCGGCCT
	GCCTGGCTTCCGGGA	CGAGCCGGAGGAGCT	GGACCCCCTCGGCCTC
25	CCTGGCTTCCGGGAG	GAGCCGGAGGAGCTG	GACCCCCTCGGCCTCC
	CTGGCTTCCGGGAGG	AGCCGGAGGAGCTGG	ACCCCCTCGGCCTCCT
	TGGCTTCCGGGAGGT	GCCGGAGGAGCTGGA	CCCCTCGGCCTCCTC
	GGCTTCCGGGAGGTC	CCGGAGGAGCTGGAC	CCCTCGGCCTCCTCG
	GCTTCCGGGAGGTCT	CGGAGGAGCTGGACC	CCTCGGCCTCCTCGT
30	CTTCCGGGAGGTCTC	GGAGGAGCTGGACCT	CTCGGCCTCCTCGTC
	TTCCGGGAGGTCTCC	GAGGAGCTGGACCTG	TCGGCCTCCTCGTCC
	TCCGGGAGGTCTCCT	AGGAGCTGGACCTGG	CGGCCTCCTCGTCCT
	CCGGGAGGTCTCCTT	GGAGCTGGACCTGGA	GGCCTCCTCGTCCTC
	CGGGAGGTCTCCTTC	GAGCTGGACCTGGAG	GCCTCCTCGTCCTCC
35	GGGAGGTCTCCTTCT	AGCTGGACCTGGAGC	CCTCCTCGTCCTCCC
	GGAGGTCTCCTTCTA	GCTGGACCTGGAGCC	CTCCTCGTCCTCCCT
	GAGGTCTCCTTCTAC	CTGGACCTGGAGCCA	TCCTCGTCCTCCCTG
	AGGTCTCCTTCTACT	TGGACCTGGAGCCAG	CCTCGTCCTCCCTGC
	GGTCTCCTTCTACTA	GGACCTGGAGCCAGA	CTCGTCCTCCCTGCC
40	GTCTCCTTCTACTAC	GACCTGGAGCCAGAG	TCGTCTCCTCCCTGCC
	TCTCCTTCTACTACA	ACCTGGAGCCAGAGA	CGTCCTCCCTGCCAC
	CTCCTTCTACTACAG	CCTGGAGCCAGAGAA	GTCTCCTCCCTGCCACT
	TCCTTCTACTACAGC	CTGGAGCCAGAGAAC	TCCTCCTCCCTGCCACTG
	CCTTCTACTACAGCG	TGGAGCCAGAGAAC	CCTCCTCCCTGCCACTGC
45	CTTCTACTACAGCGA	GGAGCCAGAGAACAT	CTCCTCCCTGCCACTGCC
	TTCTACTACAGCGAG	GAGCCAGAGAACATG	TCCCTGCCACTGCCC
	TCTACTACAGCGAGG	AGCCAGAGAACATGG	CCCTGCCACTGCCCCG
	CTACTACAGCGAGGA	GCCAGAGAACATGGA	CCTGCCACTGCCCCGA
	TACTACAGCGAGGAG	CCAGAGAACATGGAG	CTGCCACTGCCCCGAC
50	ACTACAGCGAGGAGA	CAGAGAACATGGAGA	TGCCACTGCCCCGACA
	CTACAGCGAGGAGAA	AGAGAACATGGAGAG	GCCACTGCCCCGACAG

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	CCACTGCCCCGACAGA	GGGGTGCTGGTCCTC	ATGAACGGGGGGCCGC
	CACTGCCCCGACAGAC	GGGTGCTGGTCCTCC	TGAACGGGGGGCCGCA
	ACTGCCCCGACAGACA	GGTGCTGGTCCTCCG	GAACGGGGGGCCGCAA
	CTGCCCCGACAGACAC	GTGCTGGTCCTCCGC	AACGGGGGGCCGCAAG
5	TGCCCCGACAGACACT	TGCTGGTCCTCCGCG	ACGGGGGGCCGCAAGA
	GCCCCGACAGACACTC	GCTGGTCCTCCGCGC	CGGGGGGGCCGCAAGAA
	CCCGACAGACACTCA	CTGGTCCTCCGCGCC	GGGGGGCCGCAAGAAC
	CCGACAGACACTCAG	TGGTCCTCCGCGCCA	GGGGCCGCAAGAACG
	CGACAGACACTCAGG	GGTCCTCCGCGCCAG	GGGCCGCAAGAACGA
10	GACAGACACTCAGGA	GTCCTCCGCGCCAGC	GGCCGCAAGAACGAG
	ACAGACACTCAGGAC	TCCTCCGCGCCAGCT	GCCGCAAGAACGAGC
	CAGACACTCAGGACA	CCTCCGCGCCAGCTT	CCGCAAGAACGAGCG
	AGACACTCAGGACAC	CTCCGCGCCAGCTTC	CGCAAGAACGAGCGG
	GACACTCAGGACACA	TCCGCGCCAGCTTCG	GCAAGAACGAGCGGG
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	CACTCAGGACACAAG	CGCGCCAGCTTCGAC	AAGAACGAGCGGGCC
	ACTCAGGACACAAGG	GCGCCAGCTTCGACG	AGAACGAGCGGGCCT
	CTCAGGACACAAGGC	CGCCAGCTTCGACGA	GAACGAGCGGGCCTT
	TCAGGACACAAGGCC	GCCAGCTTCGACGAG	AACGAGCGGGCCTTG
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	AGGACACAAGGCCGA	CAGCTTCGACGAGAG	GAGCGGGCCTTGCCG
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	GACACAAGGCCGAGA	GCTTCGACGAGAGAC	GCGGGCCTTGCCGCT
	ACACAAGGCCGAGAA	CTTCGACGAGAGACA	CGGGCCTTGCCGCTG
25	CACAAGGCCGAGAAC	TTCGACGAGAGACAG	GGGCCTTGCCGCTGC
	ACAAGGCCGAGAACG	TCGACGAGAGACAGC	GGCCTTGCCGCTGCC
	CAAGGCCGAGAACGG	CGACGAGAGACAGCC	GCCTTGCCGCTGCCC
	AAGGCCGAGAACGGC	GACGAGAGACAGCCT	CCTTGCCGCTGCCCC
	AGGCCGAGAACGGCC	ACGAGAGACAGCCTT	CTTGCCGCTGCCCCA
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	GCCGAGAACGGCCCC	GAGAGACAGCCTTAC	TGCCGCTGCCCCAGT
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	CGAGAACGGCCCCGG	GAGACAGCCTTACGC	CCGCTGCCCCAGTCT
	GAGAACGGCCCCGGC	AGACAGCCTTACGCC	CGCTGCCCCAGTCTT
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	ACGGCCCCGGCCCTG	AGCCTTACGCCCACA	GCCCCAGTCTTCGAC
	CGGCCCCGGCCCTGG	GCCTTACGCCCACAT	CCCCAGTCTTCGACC
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	GCCCCGGCCCTGGGG	CTTACGCCCACATGA	CCAGTCTTCGACCTG
	CCCCGGCCCTGGGGT	TTACGCCCACATGAA	CAGTCTTCGACCTGC
	CCCGGCCCTGGGGTG	TACGCCCACATGAAC	AGTCTTCGACCTGCT
	CCGGGCCCTGGGGTGC	ACGCCCACATGAACG	GTCTTCGACCTGCTG
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	GGCCCTGGGGTGCTG	GCCCACATGAACGGG	CTTCGACCTGCTGAT
	GCCCTGGGGTGCTGG	CCCACATGAACGGGG	TTCGACCTGCTGATC
	CCCTGGGGTGCTGGT	CCACATGAACGGGGG	TCGACCTGCTGATCC
	CCTGGGGTGCTGGTC	CACATGAACGGGGGC	CGACCTGCTGATCCT
50	CTGGGGTGCTGGTCC	ACATGAACGGGGGCC	GACCTGCTGATCCTT
	TGGGGTGCTGGTCCT	CATGAACGGGGGCCG	

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ACCTGCTGATCCTTG	GCGCAGCGGGGTGGG	TCCTGTACCTCAGTG
CCTGCTGATCCTTGG	CGCAGCGGGGTGGGG	CCTGTACCTCAGTGG
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TGCTGATCCTTGGAT	CAGCGGGGTGGGGGG	TGTACCTCAGTGGAT
5 GCTGATCCTTGGATC	AGCGGGGTGGGGGGG	GTACCTCAGTGGATC
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10 TCCTTGGATCCTGAA	GGTGGGGGGGGGAGAG	TCAGTGGATCTTCAG
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TGCAAACAGTAACGT	TTTTAACAATCCATT	GCCCCTTGCTGCCCCG
30 GCAAACAGTAACGTG	TTTAACAATCCATTC	CCCTTGCTGCCCCGCG
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GCACGCGCAGCGGGG	AGCCTCCTGTACCTC	GACAGCTTCTCTGCA
CACGCGCAGCGGGGT	GCCTCCTGTACCTCA	ACAGCTTCTCTGCAG
50 ACGCGCAGCGGGGTG	CCTCCTGTACCTCAG	CAGCTTCTCTGCAGT
CGCGCAGCGGGGTGG	CTCCTGTACCTCAGT	AGCTTCTCTGCAGTA

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GCTTCTCTGCAGTAA	CAGCTTTTTTATTCCC	CTTAATGACAACACT
CTTCTCTGCAGTAAA	AGCTTTTTTATTCCCT	TTAATGACAACACTT
TTCTCTGCAGTAAAA	GCTTTTTTATTCCCTG	TAATGACAACACTTA
TCTCTGCAGTAAAAC	CTTTTTTATTCCCTGC	AATGACAACACTTAA
5 CTCTGCAGTAAAACA	TTTTTATTCCCTGCC	ATGACAACACTTAAT
TCTGCAGTAAAACAC	TTTTTATTCCCTGCCC	TGACAACACTTAATA
CTGCAGTAAAACACA	TTTATTCCCTGCCCCA	GACAACACTTAATAG
TGCAGTAAAACACAT	TTATTCCCTGCCCCAA	ACAACACTTAATAGC
GCAGTAAAACACATT	TATTCCCTGCCCCAAA	CAACACTTAATAGCA
10 CAGTAAAACACATTT	ATTCCCTGCCCCAAAC	AACACTTAATAGCAA
AGTAAAACACATTTG	TTCCCTGCCCCAAACC	ACACTTAATAGCAAC
GTAAAACACATTTGG	TCCCTGCCCCAAACCC	CACTTAATAGCAACA
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15 AAACACATTTGGGAT	CTGCCCCAAACCCTTA	TTAATAGCAACAGAG
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20 CATTTGGGATGTTCC	CAAACCCTTAACTGA	AGCAACAGAGCACTT
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45 ATGCAAGCAGCTTTT	TAAGAACCTTAATGA	CTCCTCACTCTGTCC
TGCAAGCAGCTTTTT	AAGAACCTTAATGAC	TCCTCACTCTGTCCC
GCAAGCAGCTTTTTA	AGAACCCTTAATGACA	CCTCACTCTGTCCCT
CAAGCAGCTTTTTAT	GAACCTTAATGACAA	CTCACTCTGTCCCTG
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50 AGCAGCTTTTTATTTC	ACCTTAATGACAACA	CACTCTGTCCCTGTG
GCAGCTTTTTATTCC	CCTTAATGACAACAC	ACTCTGTCCCTGTCC

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CTCTGTCCCTGTCCT	AACGGAAAAATAATT	TGAGGAAGTGGCTGT
TCTGTCCCTGTCCTT	ACGGAAAAATAATTG	GAGGAAGTGGCTGTC
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TGTCCCTGTCCTTCC	GGAAAAATAATTGCC	GGAAGTGGCTGTCCC
5 GTCCCTGTCCTTCCC	GAAAAATAATTGCCA	GAAGTGGCTGTCCCT
TCCCTGTCCTTCCCT	AAAAATAATTGCCAC	AAGTGGCTGTCCCTG
CCCTGTCCTTCCCTG	AAAATAATTGCCACA	AGTGGCTGTCCCTGT
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10 TGTCCCTTCCCTGTTT	ATAATTGCCACAAGT	GGCTGTCCCTGTGGC
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15 TTCCCTGTTCTCCCT	TGCCACAAGTCCAGC	TCCCTGTGGCCCCAT
TCCCTGTTCTCCCTT	GCCACAAGTCCAGCT	CCCTGTGGCCCCATC
CCCTGTTCTCCCTTT	CCACAAGTCCAGCTG	CCTGTGGCCCCATCC
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CTGTTCTCCCTTTCT	ACAAGTCCAGCTGGG	TGTGGCCCCATCCAA
20 TGTTCTCCCTTTCTC	CAAGTCCAGCTGGGA	GTGGCCCCATCCAAC
GTTCTCCCTTTCTCT	AAGTCCAGCTGGGAA	TGGCCCCATCCAACC
TTCTCCCTTTCTCTC	AGTCCAGCTGGGAAG	GGCCCCATCCAACCA
TCTCCCTTTCTCTCT	GTCCAGCTGGGAAGC	GCCCCATCCAACCAC
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25 TCCCTTTCTCTCTCC	CCAGCTGGGAAGCCC	CCCATCCAACCACTG
CCCTTTCTCTCTCCT	CAGCTGGGAAGCCCT	CCATCCAACCACTGT
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30 TTCTCTCTCCTCTCT	TGGGAAGCCCTTTTT	CCAACCACTGTACAC
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CATAACGGAAAAATA	GTTTGAGGAAGTGGC	GCCTGACACCGTGGG
50 ATAACGGAAAAATAA	TTTGAGGAAGTGGCT	CCTGACACCGTGGGT
TAACGGAAAAATAAT	TTGAGGAAGTGGCTG	CTGACACCGTGGGTC

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TGACACCGTGGGTCA	TTATCTTTCACCTTT	CCAAGGCTGTTACCA
GACACCGTGGGTCAT	TATCTTTCACCTTTC	CAAGGCTGTTACCAT
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5 ACCGTGGGTCATTAC	CTTTCACCTTTCTAG	GGCTGTTACCATTTT
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10 GGGTCATTACAAAAA	ACCTTTCTAGGGACA	TTACCATTTTAAACGC
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20 AAAAAAACACGTGGA	GGACATGAAATTTAC	AACGCTGCCTAATTTT
AAAAAACACGTGGAG	GACATGAAATTTACA	ACGCTGCCTAATTTTG
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30 GTGGAGATGGAAATT	TTTACAAAGGGCCAT	ATTTTGCCAAAAATCC
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40 AAATTTTTTACCTTTA	GCCATCGTTCATCCA	AATCCTGAACTTCTC
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50 CTTTATCTTTTACCT	ATCCAAGGCTGTTAC	
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TTCTCCCTCATCGGC	GCATGGCAGCTGGTT	CCATCCGACTGCCCC
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CGGCCCCGGCGCTGAT	GGTTGCTCCATTTGA	CCCCTGCTGTGCTGC
GGCCCCGGCGCTGATT	GTTGCTCCATTTGAG	CCCTGCTGTGCTGCT
GCCCCGGCGCTGATTC	TTGCTCCATTTGAGA	CCTGCTGTGCTGCTC
15 CCCGGCGCTGATTCC	TGCTCCATTTGAGAG	CTGCTGTGCTGCTCA
CCGGCGCTGATTCCT	GCTCCATTTGAGAGA	TGCTGTGCTGCTCAA
CGGCGCTGATTCCTC	CTCCATTTGAGAGAC	GCTGTGCTGCTCAAG
GGCGCTGATTCCTCG	TCCATTTGAGAGACA	CTGTGCTGCTCAAGG
GCGCTGATTCCTCGT	CCATTTGAGAGACAC	TGTGCTGCTCAAGGC
20 CGCTGATTCCTCGTG	CATTTGAGAGACACG	GTGCTGCTCAAGGCC
GCTGATTCCTCGTGT	ATTTGAGAGACACGC	TGCTGCTCAAGGCCA
CTGATTCCTCGTGTC	TTTGAGAGACACGCT	GCTGCTCAAGGCCAC
TGATTCCTCGTGTC	TTGAGAGACACGCTG	CTGCTCAAGGCCACA
GATTCCTCGTGTCG	TGAGAGACACGCTGG	TGCTCAAGGCCACAG
25 ATTCCTCGTGTCGG	GAGAGACACGCTGGC	GCTCAAGGCCACAGG
TTCTCTCGTGTCGGA	AGAGACACGCTGGCG	CTCAAGGCCACAGGC
TCCTCGTGTCGGAG	GAGACACGCTGGCGA	TCAAGGCCACAGGCA
CCTCGTGTCGGAGG	AGACACGCTGGCGAC	CAAGGCCACAGGCAC
CTCGTGTCGGAGGC	GACACGCTGGCGACA	AAGGCCACAGGCACA
30 TCGTGTCGGAGGCA	ACACGCTGGCGACAC	AGGCCACAGGCACAC
CGTGTCGGAGGCAT	CACGCTGGCGACACA	GGCCACAGGCACACA
GTGTCCGGAGGCATG	ACGCTGGCGACACAC	GCCACAGGCACACAG
TGTCCGGAGGCATGG	CGCTGGCGACACACT	CCACAGGCACACAGG
GTCCGGAGGCATGGG	GCTGGCGACACACTC	CACAGGCACACAGGT
35 TCCGGAGGCATGGGT	CTGGCGACACACTCC	ACAGGCACACAGGTC
CCGGAGGCATGGGTG	TGGCGACACACTCCG	CAGGCACACAGGTCT
CGGAGGCATGGGTGA	GGCGACACACTCCGT	AGGCACACAGGTCTC
GGAGGCATGGGTGAG	GCGACACACTCCGTC	GGCACACAGGTCTCA
GAGGCATGGGTGAGC	CGACACACTCCGTCC	GCACACAGGTCTCAT
40 AGGCATGGGTGAGCA	GACACACTCCGTCCA	CACACAGGTCTCATT
GGCATGGGTGAGCAT	ACACACTCCGTCCAT	ACACAGGTCTCATTG
GCATGGGTGAGCATG	CACACTCCGTCCATC	CACAGGTCTCATTGC
CATGGGTGAGCATGG	AACTCCGTCCATCC	ACAGGTCTCATTGCT
ATGGGTGAGCATGGC	CACTCCGTCCATCCG	CAGGTCTCATTGCTT
45 TGGGTGAGCATGGCA	ACTCCGTCCATCCGA	AGGTCTCATTGCTTCT
GGGTGAGCATGGCAG	CTCCGTCCATCCGAC	GGTCTCATTGCTTCTG
GGTGAGCATGGCAGC	TCCGTCCATCCGACT	GTCTCATTGCTTCTGA
GTGAGCATGGCAGCT	CCGTCCATCCGACTG	TCTCATTGCTTCTGAC
TGAGCATGGCAGCTG	CGTCCATCCGACTGC	CTCATTGCTTCTGACT
50 GAGCATGGCAGCTGG	GTCCATCCGACTGCC	CATTGCTTCTGACTA
AGCATGGCAGCTGGT	TCCATCCGACTGCCC	

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ATTGCTTCTGACTAG	CTCTCAGTGAAGGTG
TTGCTTCTGACTAGA	TCTCAGTGAAGGTGG
TGCTTCTGACTAGAT	CTCAGTGAAGGTGGG
GCTTCTGACTAGATT	TCAGTGAAGGTGGGG
5 CTTCTGACTAGATTA	CAGTGAAGGTGGGGA
TTCTGACTAGATTAT	AGTGAAGGTGGGGAG
TCTGACTAGATTATT	GTGAAGGTGGGGAGA
CTGACTAGATTATTA	TGAAGGTGGGGAGAA
TGACTAGATTATTAT	GAAGGTGGGGAGAAG
10 GACTAGATTATTATT	AAGGTGGGGAGAAGC
ACTAGATTATTATTT	AGGTGGGGAGAAGCT
CTAGATTATTATTTG	GGTGGGGAGAAGCTG
TAGATTATTATTTGG	GTGGGGAGAAGCTGA
AGATTATTATTTGGG	TGGGGAGAAGCTGAA
15 GATTATTATTTGGGG	GGGGAGAAGCTGAAC
ATTATTATTTGGGGG	GGGAGAAGCTGAACC
TTATTATTTGGGGGA	GGAGAAGCTGAACCG
TATTATTTGGGGGAA	GAGAAGCTGAACCGG
ATTATTTGGGGGAAC	AGAAGCTGAACCGGC
20 TTATTTGGGGGAACT	
TATTTGGGGGAACTG	
ATTTGGGGGAACTGG	
TTTGGGGGAACTGGA	
TTGGGGGAACTGGAC	
25 TGGGGGAACTGGACA	
GGGGGAACTGGACAC	
GGGGAACTGGACACA	
GGGAACTGGACACAA	
GGAACCTGGACACAAT	
30 GAACTGGACACAATA	
AACTGGACACAATAG	
ACTGGACACAATAGG	
CTGGACACAATAGGT	
TGGACACAATAGGTC	
35 GGACACAATAGGTCT	
GACACAATAGGTCTT	
ACACAATAGGTCTTT	
CACAATAGGTCTTTC	
ACAATAGGTCTTTCT	
40 CAATAGGTCTTTCTC	
AATAGGTCTTTCTCT	
ATAGGTCTTTCTCTC	
TAGGTCTTTCTCTCA	
AGGTCTTTCTCTCAG	
45 GGTCTTTCTCTCAGT	
GTCTTTCTCTCAGTG	
TCTTTCTCTCAGTGA	
CTTTCTCTCAGTGAA	
TTTCTCTCAGTGAAG	
50 TTCTCTCAGTGAAGG	
TCTCTCAGTGAAGGT	

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**EXAMPLE 9**

Sub-confluent HaCaT cells were treated as described above with phosphorothioate oligonucleotides IGFR.AS (antisense: 5'-ATCTCTCCGCTTCCTTTC-3'; (<400>10); ref 5 13) and IGFR.S (sense control: 5'-GAAAGGAAGCGGAGAGAT-3'; (<400>11); ref 13) IGF-I binding to the cell monolayers was then measured as <sup>125</sup>I-IGF-I.

**EXAMPLE 10**

The results of this experiment are shown in Figures 7 and 8.

10

HaCaT cells were initially plated in DMEM with 10% v/v serum, then AS oligo experiments were performed in complete "Keratinocyte-SFM" (Gibco) to exclude the influence of exogenous IGFBPs. Oligos were synthesised as phosphorothioate (nuclease-resistant) derivatives (Bresatec, South Australia) and were as follows: antisense: AS2, 5'-  
15 GCGCCCGCTGCATGACGCCTGCAAC-3' (IGFBP-3 start codon); controls: AS2NS, 5'-CGGAGATGCCGCATGCCAGCGCAGG-3'; AS4,  
5'-AGGCGGCTGACGGCACTA-3'; AS4NS, 5'-GACAGCGTCGGAGCGATC-3'; IGFRAS, 5'-ATCTCTCCGCTTCCTTTC-3';  
IGFRS, 5'-GAAAGGAAGCGGAGAGAT-3'. Oligos to IGFBP-3 were based on the  
20 published sequence of Spratt *et al* [12]. AS oligos were added to HaCaT monolayers in 0.5ml medium in 24-well plates at the concentrations and addition frequencies indicated. IGFBP-3 measured in cell-conditioned medium using a dot-blot assay, adapted from the Western ligand blot method of Hossenlopp *et al* [11], in which 100µl of conditioned medium was applied to nitrocellulose filters with a vacuum dot-blot apparatus. After drying the membranes at 37°C,  
25 relative amounts of IGFBP are determined by <sup>125</sup>I-IGF-I-binding, autoradiography and computerised imaging densitometry. Triplicate wells (except in Figure 7, where duplicate wells were measured as shown) were analysed and corrected for changes in cell number per well. Relative cell number per well was determined using an amido black dye method, developed specifically for cultured monolayers of HaCaT cells [14]. Cell numbers differed  
30 by less than 10% after treatment. For oligos to the IGF receptor, receptor quantitation in

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intact HaCaT monolayers was by overnight incubation with  $^{125}\text{I}$ -IGF-I (30,000cpm/well) at 4°C.

#### EXAMPLE 11

5 Experiments involving ribozymes are generally conducted as described in International Patent Application No. WO 89/05852 and in Haselhoff and Gerlach [8]. Ribozymes are constructed with a hybridising region which is complementary in nucleotide sequence to at least part of a target RNA which, in this case, encodes IGFBP-2. Activity of ribozymes is measurable on, for example, Northern blots or using animal models such as in the nude mouse model (15; 16) 10 or the "flaky skin" mouse model (17; 18).

#### EXAMPLE 12

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGFBP-3 production. The activity of the ribozymes is determined as in Example 11.

15

#### EXAMPLE 13

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGF-1 production. The activity of the ribozymes is determined as in Example 11.

20

#### EXAMPLE 14

The methods described in Example 11 are used for the screening of ribozymes which inhibit IGF-1 production. The activity of the ribozymes is determined as in Example 11.

#### EXAMPLE 15

25 Twenty-one antisense oligonucleotides targeted to mRNA sequences encoding the IGF-1 receptor, and four random oligonucleotides were synthesized. The antisense oligonucleotides are C5-propynyl-dU, dC 15mer phosphorothioate oligodeoxyribonucleotides. In these oligonucleotides, a phosphorothioate backbone replaces the phosphodiester backbone of naturally occurring DNA. The positions of the 21 sequence specific antisense 30 oligonucleotides relative to the IGF-1 receptor mRNA structure are shown in Figure 9.

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### EXAMPLE 16

Experiments were performed to determine the uptake of the antisense oligonucleotides of Example 15 into keratinocytes. Cells of the differentiated human keratinocyte cell line, HaCaT, were incubated for 24 hours in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% (w/v) fetal calf serum (FCS) containing fluorescently labelled oligonucleotide (R451, a randomized sequence oligonucleotide, 30nM) and cytofectin GSV (2 $\mu$ g/ml, Glen Research, 44901 Falcon Place, Sterling, VA 20166, Cat. No. 70-3815-78). Cells were then transferred to oligonucleotide-free medium and fluorescence microscopy and phase contrast images of the cells were obtained. Figure 10 shows fluorescence microscopy (Panel A) and phase contrast (Panel B) images of uptake of fluorescently labelled oligonucleotide in the majority of cells in a HaCaT monolayer. The degree of uptake obtained with the cationic lipid cytofectin was far greater than the uptake obtained with the next best lipid tried, Tfx-50.

A further experiment was performed to assess the uptake and toxicity associated with the use of cytofectin GSV over five days. Confluent HaCaT keratinocytes were incubated in DMEM containing fluorescently labelled oligonucleotide R451 (30nM or 100 nM) plus cytofectin GSV (2 $\mu$ g/ml or 5 $\mu$ g/ml) over 120 hours, viewed by fluorescence microscopy, trypan blue stained, and counted. The graphs in Figure 11 depict uptake (Panel A) and toxicity (Panel B). The proportion of cells containing oligonucleotide remained high over the 120 hour period. The combination of 30 nM oligonucleotide and 2 $\mu$ g/ml GSV provided optimal uptake and minimal toxicity.

### EXAMPLE 17

The twenty-one oligonucleotides of Example 15 were then screened for their ability to inhibit IGF-I receptor mRNA levels in HaCaT cells, in accordance with the teachings herein. HaCaT cells were grown to 90% confluence in DMEM supplemented with 10% (v/v) FCS. Antisense oligonucleotides (30nM) were complexed with cytofectin GSV (2 $\mu$ g/ml) and added to the cells in the presence of serum. HaCaT keratinocytes were treated with the oligonucleotide/GSV complexes or randomized sequence oligonucleotides (R451, R766),

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liposome alone (GSV), or were left untreated (UT). Duplicate treatments were performed. Repeat additions of the oligonucleotides/GSV complex were performed at 24, 48 and 76 hours following the first addition. Total RNA was isolated as per the RNazolB protocol (Biotechx Laboratories, Inc. 6023 South Loop East, Houston, TX 77033) 96 hours following the first  
5 addition.

IGF-I receptor mRNA and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA levels were simultaneously determined by a ribonuclease (RNase) protection assay. The RNase Protection Assay kit, *in vitro* transcription kit, and IGF-I receptor and GAPDH DNA  
10 templates were obtained from Ambion, Inc. (2130 Woodward St., Houston, TX 77044). The amount of IGF-I receptor mRNA in any given sample was expressed as the amount of IGF-I receptor mRNA relative to the amount of GAPDH mRNA. Each oligonucleotide was tested in at least two separate experiments.

15 Figure 12 depicts representative results of the screening process. Panel A shows an electrophoretic analysis of IGF-I receptor and GAPDH mRNA fragments after RNase protection. Molecular weight markers are shown on the right hand side. The full-length probe is shown on the left hand side; G-probe indicates the IGF-I receptor probe. GAPDH protected fragments (G) are seen at 316 bases and IGF-I protected fragments (I) are seen at  
20 276 bases. Exhibit E, Panel B provides a graph indicating the relative level of IGF-I receptor mRNA following each treatment.

The results obtaining from the above screening assays are summarized in Figure 13. The graph depicts the relative level of IGF-I receptor mRNA after treatment with oligonucleotides  
25 complementary to the human IGF-I receptor mRNA (26-86), four randomized sequence oligonucleotides (R1, R4, R7, R9), liposome alone (GSV), or no treatment (UT). Asterisks indicate a significant different in relative IGF-I receptor mRNA as compared to GSV treated cells ( $n=4-10$ ,  $p<0.05$ ).

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As demonstrated in Figure 13, treatment with eighteen of the twenty-one oligonucleotides resulted in a significant difference in levels of IGF-I receptor mRNA relative to GSV treated cells. Three of the antisense oligonucleotides tested in the screening assay reduce IGF-I receptor mRNA to less than 35% of GSV-treated cells. These antisense oligonucleotides have the following sequences, presented in the 5' to 3' direction:

#27 UCCGGAGCCAGACUU

#64 CACAGUUGCUGCAAG

#78 UCUCCGCUUCCUUC

10

As further demonstrated in Figure 13, six of the antisense oligonucleotides tested in the screening assay reduce IGF-I receptor mRNA to between 35 and 50% of GSV-treated cells. These antisense oligonucleotides have the following sequences, presented in the 5' to 3' direction:

15

#28 AGCCCCCACAGCGAG

#32 GCCUUGGAGAUGAGC

#40 UAACAGAGGUCAGCA

#42 GGAUCAGGGACCAGU

20 #46 CGGCAAGCUACACAG

#50 GGCAGGCAGGCACAC

#### EXAMPLE 19

Another experiment was performed demonstrating that antisense oligonucleotides targeted to genetic sequences encoding the IGF1R receptor and that reduce IGF-I receptor mRNA levels also inhibit the IGF-I receptor level on the surface of the treated cultured keratinocytes. HaCaT cells were grown to confluence in 24-well plates in DMEM containing 10% (v/v) FCS. Oligodeoxynucleotide and cytofectin GSV were mixed together in serum-free DMEM, and incubated at room temperature for 10 minutes before being diluted ten-fold in medium and placed on the cells. Cells were incubated for 72 hours with 30nM random sequence or

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antisense oligonucleotide and 2  $\mu$ m/ml GSV, or with GSV alone in DMEM containing 10% (v/v) FCS with solutions replaced every 24 hours. This was followed by incubation with oligonucleotide/GSV in serum-free DMEM for 48 hours. All incubations were performed at 37°C. Cells were washed twice with 1ml cold PBS. Serum-free DMEM containing 10<sup>-7</sup> M <sup>125</sup>I-IGF-I was added with or without the IGF-I analogue, des (1-3) IGF-I, at 10<sup>-11</sup> M to 10<sup>-7</sup> M. Cells were incubated at 4°C for 17 hours with gentle shaking, then washed three times with 1ml cold PBS and lysed in 250  $\mu$ l 0.5M NaOH/0.1% (v/v) Triton X-100 at room temperature for 4 hours. Specific binding of the solubilised cell extract was measured using a gamma counter. As shown in Figure 14, treatment of HaCaT keratinocytes with oligonucleotide reduced cell surface IGF-I receptor levels to 30% of levels in untreated keratinocytes or in keratinocytes treated with liposome alone or a random oligonucleotide, R766. As shown in Figure 15, treatment with oligonucleotide #27 also significantly reduced cell surface IGF-I receptor levels relative to untreated keratinocytes or treatment with liposome alone or random nucleotide R451. As demonstrated in Example 17, oligonucleotides #64 and #27 reduce IGF-I receptor mRNA levels in cultured keratinocytes to less than 35% of GSV-treated cells. Accordingly, the ability of an oligonucleotide to reduce IGF-I receptor mRNA levels in correlated with its ability to reduce cell surface IGF-I receptor levels.

The forgoing Examples demonstrate that antisense oligonucleotides targeted to the IGF-I receptor can be delivered to human keratinocytes *in vitro*, can inhibit IGF-I receptor mRNA levels in human keratinocytes *in vitro*, and that inhibition of mRNA levels is correlated with reduction of cell surface IGF-I receptor levels.

25

#### EXAMPLE 19

Further experiments demonstrated the efficacy of antisense oligonucleotides targeted to the IGF-I receptor in an *in vivo* model of psoriasis. An animal model of psoriasis is the human psoriatic skin xenograft model. The skin used in this model contains the true disease state. In this model, reduction in epidermal thickness of psoriatic grafts in response to treatment is positively correlated with efficacy of treatment. Both normal and psoriatic human skin were

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grated into a thymic (nude) mice in accordance with a thymic (nude) mice in accordance with the methods of Baker *et al* (1992) *Brit. J. Dermatol.* 126:105 and Nanney *et al* (1992) *J. Invest. Dermatol.* 92:296. Successful grafting was achieved, as demonstrated in Figure 16, which shows hemotoxylin and eosin (H&E) stained sections of a 49-day old psoriatic human skin graft (Panel B) compared to the histology of the skin graft prior to grafting (Panel A). The histological features of psoriasis present in the pregraft section (e.g., parakeratosis, acanthosis and pronounced rete ridges) are present in the grafts more than seven weeks post grafting.

- 10 Using the model, oligonucleotide uptake was measured in epidermal keratinocytes *in vivo* after intradermal injection. Fluorescently labelled oligonucleotide (R451, 50 $\mu$ l, 10 $\mu$ M injection) was intradermally injected into psoriatic and normal skin grafts on a thymic mice. Live confocal microscopy and fluorescence microscopy of fixed sections was then employed. Using both techniques, oligonucleotide was found to localize in the nucleus of over 90% of basal keratinocytes. Figure 17 shows the nuclear localization of oligonucleotide in psoriatic skin cells using conventional fluorescence microscopy of a graft that was removed and sectioned after 24 hours.

After establishing oligonucleotide uptake in the *in vivo* model, a small number of pilots experiments were performed to determine a schedule for treatment of grafted mice with antisense oligonucleotides targeted to genetic sequences encoding the IGF-I receptor. The treatment schedule was finalized as follows:

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Graft Number	Treatment	Volume of Injection	ODN Concentration	Duration of Treatment
1-3	Vehicle (PBS)	50 $\mu$ l	-	20 days
4-6	RandomODN#R451	50 $\mu$ l	10 $\mu$ M	20 days
5 7-9	ODN#27	50 $\mu$ l	10 $\mu$ M	20 days
10-12	ODN#74	50 $\mu$ l	10 $\mu$ M	20 days
13-15	ODN#50	50 $\mu$ l	10 $\mu$ M	20 days

As determined above, oligonucleotide #27 (ODN #27) reduced IGF-I receptor mRNA *in vitro* to less than 35% of GSV-treated cells. Oligonucleotide #50 (ODN#50) reduced IGF-I receptor mRNA *in vitro* to between 35 and 50% of GSV-treated cells. Oligonucleotide #74 (ODN #74) was not inhibitory to IGF-I receptor mRNA *in vitro*. In the *in vivo* model, each mouse received two grafts. Random oligonucleotide or vehicle was injected intradermally in one graft and acted as a control. The second graft was injected with the targeted oligonucleotide. Each graft received an injection every second day for the duration of the treatment.

Histology of representative grafts from each treatment type are shown in Figures 18(a)-(d) and 19(a) - (d). Each sheet shows three images of H&E stained sections: the pregraft histology, the control treated graft, and the targeted oligonucleotide treated graft. Figures 18(a)-(d) are shown at 100x magnification; figures 19(a)-(d) are shown at 400x magnification. The total cross sectional area of epidermis of each graft was assessed using MCID analysis software. The pooled results from all of the treated grafts are shown in Figure 20.

25

As shown in Figures 18(a)-(d) and 19(a)-(d), the vehicle-treated (control) grafts were marginally thinner than the pregraft sections. The degree of regression in these experiments (ie., less than 10%) is not significant. A similar amount of marginal thinning

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of epidermis compared to pregraft also occurred in pilot experiments in which psoriatic grafts were not injected, and thus it is unlikely that the vehicle itself has any effect. Histological features of psoriasis present in skin samples prior to grafting (clubbing of rete ridges, parakeratosis, acanthosis) were present in these grafts.

5

The random oligonucleotide treated grafts varied in epidermal thickness after 20 days of treatment. Grafts were either a similar thickness to the pregraft histology, or marginally thinner. Random oligonucleotide treated grafts were in each case significantly thicker than their targeted oligonucleotide treated pairs.

10

As shown in Figure 20, the targeted oligonucleotide treated grafts were significantly thinner than the pregraft sections and showed less parakeratosis and clubbing of rete ridges. Antisense oligonucleotides which were effective at reducing IGF-I receptor mRNA levels *in vitro* (#27 and #50) produced greater epidermal thinning than an

15 oligonucleotide which was not inhibitory to IGF-I receptor mRNA *in vitro* (#74).

Accordingly, there is a direct correlation between the ability of an oligonucleotide targeted to the IGF-I receptor to inhibit IGF-I receptor mRNA levels *in vitro* and the efficacy of the oligonucleotide as an anti-psoriasis agent in an *in vivo* model.

20

#### EXAMPLE 20

Another experiment demonstrated that treatment of psoriatic grafts with an oligonucleotide targeted to a genetic sequence encoding the IGF-I receptor results in inhibition of proliferation. Pregrafts from psoriatic patients, control grafts treated with R4541, and grafts treated with oligonucleotide #27 were obtained as described in Example 19. An

25 antibody to the cell cycle-specific nuclear antigen Ki67 was used to

immunohistochemically detect actively dividing cells and thereby assess proliferation. The  $\alpha$ Ki67 antibody (DAKO, Glostrup, Denmark) recognizes the Ki67 antigen transiently expressed in nuclei of proliferating cells during late G<sub>1</sub>, S, M and G<sub>2</sub> phases of the cycle and thus provides a marker for proliferation. Pregraft and graft sections were

30 immunohistochemically processed by standard methods using  $\alpha$ Ki67 (according to the

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manufacturer's instructions), peroxidase-conjugated anti-rabbit second stage antibody, and a chromogenic peroxidase substrate.

The results of this experiment are presented in Figure 21 as immunohistochemical sections at 100x magnification. The top panel of Figure 21 depicts a pregraft section obtained from a psoriatic patient. The epidermis is thicker than normal and nucleic are evident in the stratum corneum. Ki67 positive cells, appearing as brown dots, are evidence in the basal and suprabasal layers, and indicate actively proliferating cells. The control (R450-treated) graft in the bottom panel of Figure 21 also exhibits evidence of proliferation, including parakeratosis and Ki67-positive cells appearing as brown-staining nuclei. The center panel of Figure 21 exhibits the oligonucleotide #27-treated graft. This graft exhibits significantly reduced proliferation as evidenced by normal (thin) epidermis, lack of invaginations, and substantial loss of Ki67-positive cells.

These results indicate that treatment of human psoriatic grafts with an oligonucleotide targeted to mRNA encoding the IGF-I receptor results in inhibition of epidermal proliferation.

#### EXAMPLE 21

Topical formulations of complexes of oligonucleotides with cytofectin GSV in aqueous or methylcellulose gel formulations were prepared and assessed for uptake of the oligonucleotide by keratinocytes *in vivo*. The topical formulations contained oligonucleotides complexed with cytofectin GSV in an aqueous solution or methylcellulose carrier, as taught herein. With both aqueous and methylcellulose gel formulations, localization of oligonucleotide R451 to nuclei and cytoplasm of keratinocytes in normal human skin grafts on nude mice was observed. Figure 22 shows an image from confocal microscopy demonstrating oligonucleotide localization in the nuclei and cytoplasm of keratinocytes in normal human skin grafts after topical application of fluorescently labeled oligonucleotide (10 $\mu$ M R451) complexed with cytofectin GSV (10 $\mu$ g/ml). Figure 23 shows an image from confocal microscopy demonstrating that topical application of the

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same oligonucleotide/GSV concentrations in a 3% (w/v) methylcellulose gel produced similar uptake in the target keratinocyte population. Using an aqueous formulation of oligonucleotide/GSV complexes, penetration of oligonucleotide into the viable epidermis was observed, whereas application of formulations of oligonucleotide complexed with  
5 other cationic lipids resulted in localization of oligonucleotide in the stratum corneum.

## EXAMPLE 22

Thirteen antisense oligonucleotides targeted to IGFBP-3 were synthesized. The antisense oligonucleotides are C5-propynyl-dU, Dc15 mer phosphorothioate  
10 oligodeoxyribonucleotides. Figure 24 attached hereto is a schematic diagram indicating the position of the thirteen oligonucleotides relative to the IGFBP-3 mRNA structure.

These oligonucleotides were screened for their ability to inhibit IGFBP-3 mRNA levels of HaCaT cells in accordance with the teachings herein. HaCaT cells were grown to 90%  
15 confluence in DMEM supplemented with 10% (v/v) FCS, then placed in complete keratinocyte serum free medium (KSFM, Gibco), which has a defined amount of EGF, for 24 hours. Oligonucleotides (30nM or 100nM) were complexed with GSV cytofectin (2 $\mu$ g/ml) and added to cells in complete KSFM to allow oligonucleotides to enter the nucleus before removal of EGF. Repeat additions were performed at three hours (in  
20 serum free DMEM, which releases the EGF inhibition of IGFBP-3 mRNA) and again after another 24 hours. HaCaT cells were also treated with randomized sequence oligonucleotides (R121, R451, R766 and R961), liposome alone (GSV) or were left untreated (UT). Total RNA was isolated as described in Example 17, 24 hours after the last treatment. Total RNA (15 $\mu$ g) was analyzed by Northern analysis and  
25 phosphorimager quantitation for IGFBP-3 and GAPDH mRNA. IGFBP-3 mRNA is expressed as the amount of IGFBP-3 mRNA relative to the amount of GAPDH mRNA.

Figures 25(a)-(d) provide graphs which depict results in this screening process. In these graphs, R1 and R12 refer to R121; R4, R4(0) and R45 refer to R451; R7, R7(0) and R76  
30 refer to R766; and R9 and R96 refer to R961. The values were standardized to GSV-

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- treated cells, and data was pooled and statistically analyzed by ANOVA followed by Domet's test to compare each treatment to GSV-treated cells. The pooled data are presented as a bar graph in Figure 26. As demonstrated, at a concentration of 30nM, treatment of HaCaT cells with 8 of the 12 targeted oligonucleotides tested resulted in a statistically significant reduction in levels of IGFBP-3 mRNA relative to GSV-treated cells. At a concentration of 100nM, treatment with 9 of the 13 targeted oligonucleotides tested resulted in a statistically significant reduction in levels of IGFBP-3 mRNA relative to GSV-treated cells.
- 10 These experiments demonstrate that antisense oligonucleotides targeted to genetic sequences encoding IGFBP-3 can inhibit IGFBP-3 mRNA levels in human keratinocytes *in vitro*.

### EXAMPLE 23

- 15 IGF-I receptor is a potent mitotic signalling molecule for keratinocytes and the human receptor elicits separate intracellular signals that prevent apoptosis (19). It is proposed in accordance with the present invention that inactivation of IGF-I receptors in epidermal keratinocytes will achieve three important outcomes in subsequent UV treatment of lesions:
- 20
- (i) Acute epidermal hyperplasia following UV has been suggested to increase the risk of keratinocyte carcinogenic transformation (22). By reducing IGF-I receptor expression in the epidermis, the incidence of epidermal hyperplasia following UV exposure is likely to be reduced leading to an overall acceleration in normalization of the lesion and reduced carcinogenic risk.
  - 25
  - (ii) Inhibition of anti-apoptotic action of IGF-I receptor will enhance the reversal of epidermal thickening and accelerate normalization of differentiation. Topical or injected IGF-I receptor antisense as adjunctive treatment will increase apoptosis in

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the epidermal layer thereby enhancing the reduction in acanthosis observed in UV treatments.

- (iii) Survival of keratinocytes, ie. those which evade apoptosis is likely to occur when cells have damaged DNA. Such mutations may be in the tumor suppressor region. Consequently, the use of antisense therapy will result in less frequent selection of mutated keratinocytes and therefore reduced incidence of basal cell carcinomas and squamous.
- 10 Accordingly, antisense therapy, especially against IGF-I-receptor is useful in combination with UV therapy in the treatment of epidermal hyperplasia.

#### EXAMPLE 24

HaCaT cells were treated with antisense oligonucleotides directed to IGF-I receptor mRNA. Levels of IGF-I receptor mRNA were then monitored. In essence, confluent HaCaT cells were treated every 24 hours for four days with 2  $\mu$ g/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific oligonucleotides (#26 to #86) or random sequence oligonucleotides (*R121*, *R451* and *R766*). Figure 27(a) is a photographic representation showing representative RNase protection assay gel showing IGF-I receptor (IGFR) and GAPDH mRNA in untreated or treated HaCaT cells. Figure 27(b) is a densitometric quantification of IGF-I receptor mRNA in a HaCaT cells following treatment with IGF-I receptor specific oligonucleotides (solid black) random sequence oligonucleotides (horizontal striped bar) or GSV alone (shaded bar) compared to untreated cells (UT, vertical striped bar).

25

#### EXAMPLE 25

In this example, reduction in total cellular IGF-I receptor protein was monitored following antisense oligonucleotide treatment. Confluence HaCaT cells were treated with 24 hours for 4 days with 2  $\mu$ g/ml GSV lipid alone (GSV) or complexed with 30 nM IGF-I receptor specific AONS (#27, #50 and #64) or the random sequence oligonucleotide, R451. Total

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cellular protein was isolated and analysed for IGF-I receptor by SDS PAGE followed by western blotting with antibody specific for the human IGF-I receptor. Figure 28(a) shows duplicate treated cellular extracts following the IGF-I receptor at the predicted size of 110 kD. Figure 28(b) is a densitometric quantification of IGF-I receptor protein.

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#### EXAMPLE 26

The reduction in IGF-I receptor numbers was determined on the keratinocyte cell surface after antisense oligonucleotide treatment. HaCaT cells were transfected with IGF-I receptor specific AONs #27, #50, #64, a random sequence oligonucleotides (R451) or following treatment with GSV a lipid alone every 24 hours for 4 days. Competition binding assays using  $^{125}\text{I}$ -IGF-I and the receptor-specific analogue, des(1-3)IGF-I were performed. Results are shown in Figure 29.

#### EXAMPLE 27

15 In this example, the apoptotic protecting effects of IGF-I receptor on keratinocyte cells was tested by following the reduction in keratino cell numbers following antisense oligonucleotide treatment. HaCaT cells, initially at 40% confluence, were transfected with the IGF-I receptor specific AON #64, control sequences R451 and 6414 or treated with GSV a lipid alone every 24 hours for 2 days. The cell number was measured in culture wells using a dye binding assay. The results are presented in Figure 30. The results clearly confirm that the IGF-I receptor exhibits an anti-apoptotic effect. By reducing IGF-I receptor levels using antisense oligonucleotide treatment, the anti-apoptotic effect is interrupted and apoptosis results in the reduction in keratinocyte cell number. Results are shown in Figure 30.

25

#### EXAMPLE 28

This example shows a reversal of epidermal hyperplasia in psoriatic human skin grafts on nude mice following intradermal injection with antisense oligonucleotides. Grafted psoriasis lesions were injected with IGF-I receptor specific AONs, a random sequence oligonucleotide in PBS, or with PBS alone, every 2 days for 20 days, then analysed

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histologically. The results are shown in Figure 31. In Figure 31(a), donor A graft treated with AON #50 showing epidermal thinning compared with the pregraft and control (PBS) treated graft and donor graft treated with AON #27 showing epidermal thinning compared with pregraft and control (R451) treated graft. In Figure 31(b), the mean epidermal cross-sectional area over the full width of grafts is shown as determined by digital image analysis. The results show that epidermal hyperplasia is reversed following the intradermal injection of antisense oligonucleotides.

#### EXAMPLE 29

Figure 32 shows the reversal of epidermal hyperplasia correlating with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides. Figure 32(a) shows a psoriasis lesion prior to grafting and after grafting and treatment with IGF-I receptor specific oligonucleotide #27 (AON #27) or random sequence (R451) immunostained with antibodies to Ki67 to identify proliferating cells. Proliferating cells are indicated by a dark brown nucleus (arrows). Figure 32(b) shows the same lesion prior to grafting and after oligonucleotide treatment as in Figure 32(a) but subjected to *in situ* hybridisation with <sup>35</sup>S-labelled cRNA probe complementary to the human IGF-I receptor mRNA. The presence of IGF-I receptor mRNA is indicated by silver grains which are almost eliminated in the epidermis of the lesion treated with IGF-I receptor specific oligonucleotide # 27 (AON #27). This experiment shows that reversal of epidermal hyperplasia correlates with reduced IGF-I receptor mRNA in grafted psoriasis lesions treated with antisense oligonucleotides.

#### EXAMPLE 30

Figure 33 treatment with oligonucleotides. HaCaT cell monolayers were grown to 90% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for two days with 2 µg/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Total RNA was isolated and analysed for IGF-I receptor and GAPDH mRNA using a commercially available ribonuclease protection assay kit. The results show a reduction in IGF-I receptor mRNA in the HaCaT keratinocyte cells.

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### EXAMPLE 31

Figure 34 treatment with oligonucleotides. HaCaT cell monolayers were grown to 90% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for 4 days with 2  $\mu$ g/ml GSV lipid alone (GSV) or complexed with 30 nM oligonucleotide. Cells  
5 were lysed in a buffer containing 50 mM HEPES, 150 mM NaCl, 10% v/v glycerol, 1 v/v Trison X-100 and 100  $\mu$ g/ml aprotinin on ice for 30 minutes, then 30  $\mu$ g of lysate was loaded onto a denaturing 7% w/v polyacrylamide gel followed by transfer onto an Immobilon-P membrane. Membranes were then incubated with anti-IGF-I receptor antibodies C20 (available from Santa Cruz Biotechnology Inc., Santa Cruz, California) for  
10 1 hour at room temperature and developed using the Vistra ECF western blotting kit (Amersham). The results shown in Figure 34 confirm that IGF-I receptor protein is reduced in HaCaT keratinocytes following treatment with oligonucleotides.

### EXAMPLE 32

15 This example shows a reduction in HaCaT keratinocyte cell number following treatment with oligonucleotides. The results are shown in Figure 35. HaCaT cell monolayers were grown at 40% confluence in DMEM containing 10% fetal calf serum treated every 24 hours for 3 days with 2  $\mu$ g/ml GSV lipid alone (GSV) or complexed with 15 nM oligonucleotide. Cell numbers were then measured every 24 hours using the amido black  
20 dye binding assay [32]. Results show that HaCaT keratino cells decrease in number following treatment with oligonucleotides due to a reduction in the anti-apoptotic effect of the IGF-I receptor.

Those skilled in the art will appreciate that the invention described herein is susceptible to  
25 variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

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CLAIMS:

1. A method for ameliorating the effects of a medical disorder such as a proliferative and/or inflammatory skin disorder in a mammal, said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation or a cell otherwise involved with said medical disorder with an effective amount of a nucleic acid molecule or chemical analogue thereof capable of inhibiting or otherwise reducing growth factor mediated cell proliferation and/or inflammation and/or other medical disorders.
2. A method according to claim 1 wherein cell proliferation and/or inflammation or other medical disorder is mediated by at least one of insulin-like growth factor I (IGF-I), keratinocyte growth factor (KGF), transforming growth factor- $\alpha$  (TGF $\alpha$ ), tumour necrosis factor- $\alpha$  (TNF $\alpha$ ), interleukin (IL) -1 (IL-1), IL-4, IL-6, IL-8 and/or basic fibroblast growth factor (bFGF).
3. A method according to claim 2 wherein cell proliferation and/or inflammation or other medical disorder is mediated by IGF-I.
4. A method according to claim 1 wherein the nucleic acid molecule inhibits or otherwise reduces IGF-I mediated cell proliferation and/or inflammation or other medical disorder.
5. A method according to claim 1 wherein the proliferative or inflammatory skin disorder is psoriasis, ichthyosis, pityriasis, rubra, pilaris, seborrhoea, keloids, keratosis, neoplasias, scleroderma, warts, benign growths or cancers of the skin.
6. A method according to claim 5 wherein the skin condition is psoriasis.

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7. A method according to claim 1 wherein the other medical disorder is a hyperneovascular condition such as a neovascular condition of the retina, brain or skin, growth factor-mediated malignancies, other sclerotic disease, kidney disease or hyperproliferation of the inside of blood vessels or any other hyperplasia.
8. A method according to claim 1 or 4 or 6 or 7 wherein the mammal is a human.
9. A method according to claim 1 or 4 or 6 or 7 wherein the nucleic acid molecule is capable of inhibiting, reducing or otherwise interfering with IGF-I-interaction with its receptor.
10. A method according to claim 9 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGF-I, IGF-I-receptor or an IGF binding protein (IGFBP).
11. A method according to claim 10 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGFBP-2, -3, -4, -5 or -6.
12. A method according to claim 11 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGFBP-2 or IGFBP-3.
13. A method according to claim 10 or 12 wherein the antisense molecule is at least about 15 nucleotides in length and is capable of interacting with at least one sequence selected from the list set forth in Example 6 or Example 7 or Example 8.
14. A method according to claim 12 wherein the antisense molecule comprises the nucleotide sequence:

5'-ATCTCTCCGCTTCCTTTC-3' (<400>10)

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15. A method according to claim 12 wherein the antisense molecule is selected from the following:

UCCGGAGCCAGACUU (<400>12)

CACAGUUGCUGCAAG (<400>13)

UCUCCGCUUCCUUUC (<400>14)

AGCCCCCACAGCGAG (<400>15)

GCCUUGGAGAUGAGC (<400>16)

UACAGAGGUCAGCA (<400>17)

GGAUCAGGGACCAGU (<400>18)

CGGCAAGCUACACAG (<400>19)

GGCAGGCAGGCACAC (<400>20)

16. A method according to claim 15 wherein the antisense molecule in <400>12, <400>13 or <400>14.
17. A method according to claim 15 wherein the antisense molecule in <400>12.
18. A nucleic acid molecule comprising at least about 10 nucleotides capable of hybridising to or forming a heteroduplex or otherwise interacting with a complementary form of <400>12 to <400>20 inclusive.
19. A nucleic acid molecule comprising at least about 15 nucleotides capable of hybridising to or form a heteroduplex or otherwise interacting with a complementary form of <400>12 to <400>14 inclusive.
20. A method of ameliorating the effects of psoriasis or other medical disorder, said method comprising contacting proliferating skin or skin capable of proliferation or cell otherwise associated with said medical disorder with an effective amount of one or more nucleic acid molecules or chemical analogues thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation other medical disorder



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wherein said one or more molecules comprises a polynucleotide capable of interacting with mRNA directed from an IGF-I gene, an IGF-I receptor gene or a gene encoding an IGFBP.

21. A method according to claim 20 wherein the IGFBP is IGFBP-2 or IGFBP-3.
22. A method according to claim 20 or 21 wherein the mammal is a human.
23. A method according to claim 22 wherein the nucleic acid molecule is capable of interacting with a nucleotide sequence selected from the list set forth in <400>12 to <400>14 inclusive.
24. A method according to claim 23 wherein the nucleic acid molecule comprises the nucleotide sequence selected from <400>12 to <400>14.
25. A composition comprising a nucleic acid molecule capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation or other medical disorder said composition further comprising one or more pharmaceutically acceptable carriers and/or diluents.
26. A composition according to claim 25 wherein the nucleic acid molecule is antisense molecule to a gene encoding IGF-I, IGF-I-receptor or an IGFBP.
27. A composition according to claim 26 wherein the nucleic acid molecule is selected from <400>12 to <400>20 inclusive.
28. A composition according to claim 26 selected from <400>12 to <400>14 inclusive.
29. A method for ameliorating the effects of a proliferative and/or inflammatory skin disorder such as psoriasis said method comprising contacting the proliferating and/or inflamed skin or skin capable of proliferation and/or inflammation with effective amounts of UV treatment and a nucleic acid molecule or chemical

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analogue thereof capable of inhibiting or otherwise reducing IGF-I mediated cell proliferation and/or inflammation.

30. A method according to claim 29 wherein the proliferative or inflammatory skin disorder is psoriasis, ichthyosis, pityriasis, rubra, pilaris, seborrhoea, keloids, keratosis, neoplasias, scleroderma, warts, benign growths or cancers of the skin.
31. A method according to claim 30 wherein the proliferative or inflammatory skin disorder is psoriasis.
32. A method according to claim 29 or 30 or 31 wherein the nucleic acid molecule is capable of inhibiting, reducing or otherwise interfering with IGF-I-interaction with its receptor.
33. A method according to claim 32 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGF-I, IGF-I-receptor or an IGF binding protein (IGFBP).
34. A method according to claim 33 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGFBP-2, -3, -4, -5 or -6.
35. A method according to claim 34 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGFBP-2 or IGFBP-3.
36. A method according to claim 33 wherein the nucleic acid molecule is an antisense molecule capable of reducing expression of a gene encoding IGF-I receptor.
37. A method according to any one of claims 29 to 36 wherein the antisense molecule is at least about 15 nucleotides in length and is capable of interacting with at least one sequence selected from the list set forth in Example 6 or Example 7 or Example 8.

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38. A method according to claim 37 wherein the antisense molecule comprises the nucleotide sequence:

5'-ATCTCTCCGCTTCCTTTC-3' (<400>10)

39. A method according to claim 37 wherein the antisense molecule is selected from the following:

UCCGGAGCCAGACUU (<400>12)

CACAGUUGCUGCAAG (<400>13)

UCUCCGCUUCCUUUC (<400>14)

AGCCCCACAGCGAG (<400>15)

GCCUUGGAGAUGAGC (<400>16)

UACAGAGGUCAGCA (<400>17)

GGAUCAGGGACCAGU (<400>18)

CGGCAAGCUACACAG (<400>19)

GGCAGGCAGGCACAC (<400>20)

40. A method according to claim 39 wherein the antisense molecule in <400>12, <400>13 or <400>14.
41. A method according to claim 40 wherein the antisense molecule in <400>12.
42. A method according to claim 39 wherein the UV treatment occurs simultaneously with or following contact with the nucleic acid molecule or its chemical analogue.
43. Use of an antisense molecule directed to the gene encoding IGF-I receptor or its mRNA as adjunct therapy in combination with UV treatment to reduce proliferation and/or inflammation of keratinocyte cells.
44. Use according to claim 43 in the treatment of psoriasis.

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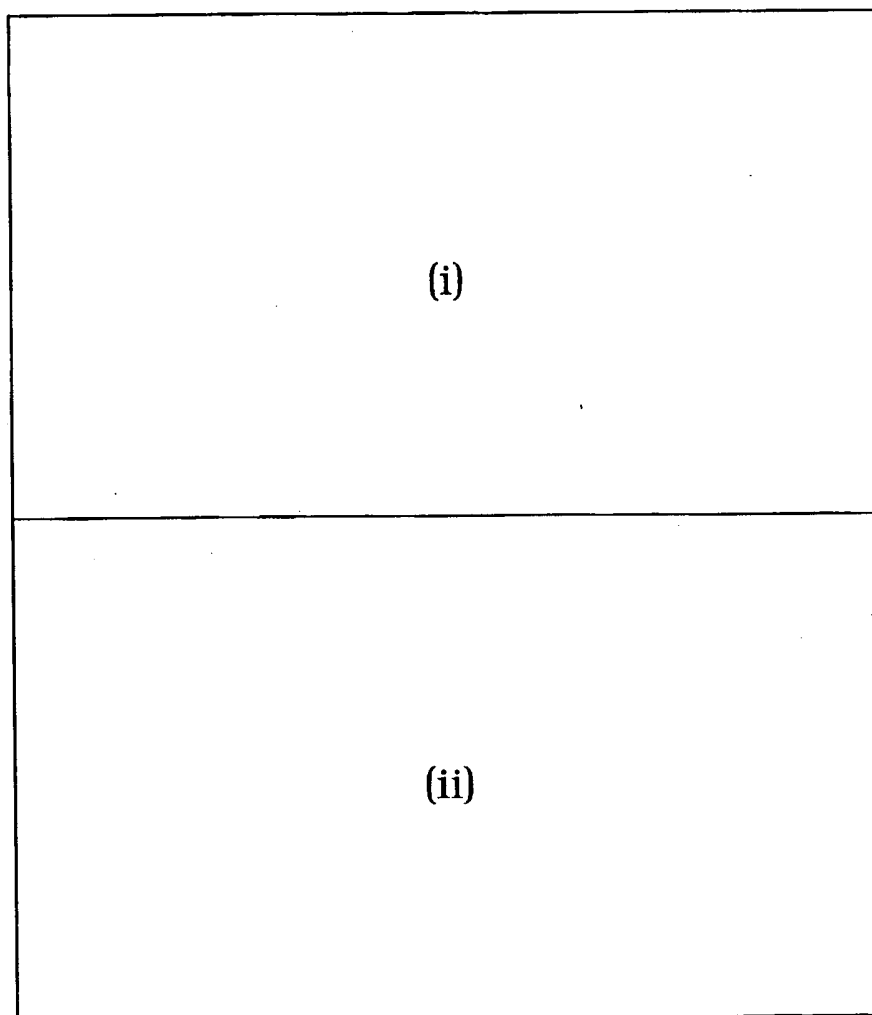


Figure 1

Substitute Sheet  
(Rule 26) RO/AU

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1	ATTCGGGGCG	AGGAGGAGG	AAGAAGCGGA	GGAGGCGGCT	CCCGCTCGCA
51	GGGCCGTGCA	CCTGCCCGCC	CGCCCGCTCG	CTCGCTCGCC	CGCCGCGCCG
101	CGCTGCCGAC	CGCCAGCATG	CTGCCGAGAG	TGGGCTGCCC	CGCGCTGCCG
151	CTGCCGCCGC	CGCCGCTGCT	GCCGCTGCTG	CCGCTGCTGC	TGCTGCTACT
201	GGGCGCGAGT	GGCGGCGGCG	GCGGGGCGCG	CGCGGAGGTG	CTGTTCCGCT
251	GCCCCGCCCTG	CACACCCGAG	CGCCTGGCCG	CCTGCGGGCC	CCCGCCGGTT
301	GCGCCGCCCG	CCGCGGTGGC	CGCAGTGGCC	GGAGGCGCCC	GCATGCCATG
351	CGCGGAGCTC	GTCCGGGAGC	CGGGCTGCGG	CTGCTGCTCG	GTGTGCGCCC
401	GGCTGGAGGG	CGAGGCGTGC	GGCGTCTACA	CCCCGCGCTG	CGGCCAGGGG
451	CTGCGCTGCT	ATCCCCACCC	GGGCTCCGAG	CTGCCCCCTGC	AGGCGCTGGT
501	CATGGGCGAG	GGCACTTGTG	AGAAGCGCCG	GGACGCCGAG	TATGGCGCCA
551	GCCCCGGAGCA	GTTGCAGAC	AATGGCGATG	ACCACTCAGA	AGGAGGCCTG
601	GTGGAGAACC	ACGTGGACAG	CACCATGAAC	ATGTTGGCG	GGGAGGCAG
651	TGCTGGCCCG	AAGCCCCTCA	AGTCGGGTAT	GAAGGAGCTG	GCCGTGTCC
701	GGGAGAAGGT	CACTGAGCAG	CACCGGCAGA	TGGGCAAGGG	TGGCAAGCAT

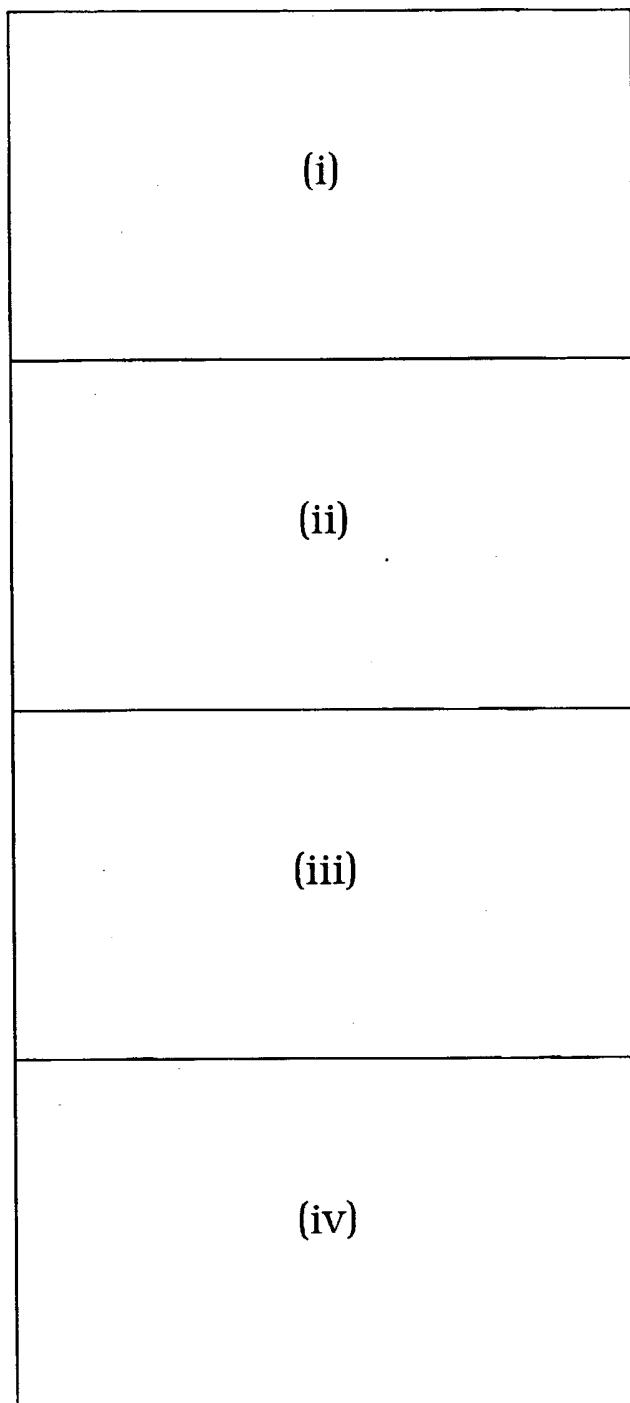
Figure 1(i)

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751 CACCTTGGCC TGGAGGAGCC CAAGAAGCTG CGACCACCCC CTGCCAGGAC  
801 TCCCTGCCAA CAGGAACTGG ACCAGGTCCT GGAGCGGATC TCCACCATGC  
851 GCCTTCCGGA TGAGCGGGC CCTCTGGAGC ACCTCTACTC CCTGCACATC  
901 CCCAACTGTG ACAAGCATGG CCTGTACAAC CTCAAAACAGT GCAAGATGTC  
951 TCTGAACGGG CAGCGTGGG AGTGCTGGTG TGTGAACCCC AACACCGGGA  
1001 AGCTGATCCA GGGAGCCCC ACCATCCGGG GGGACCCCGA GTGTCACTC  
1051 TTCTACAATG AGCAGCAGGA GGCTTGCGGG GTGCACACCC AGCGGATGCA  
1101 GTAGACCGCA GCCAGCCGGT GCCTGGCGCC CCTGCCCCCC GCCCCTCTCC  
1151 AAACACCGC AGAAACGGA GAGTGCTTGG GTGGTGGTG CTGGAGGATT  
1201 TTCCAGTTCT GACACACGTA TTTATATTG GAAAGAGACC AGCACCGAGC  
1251 TCGGCACCTC CCCGGCCTCT CTCCTCCCAG CTGCAGATGC CACACCTGCT  
1301 CCTTCTTGCT TTCCCCGGG GAGGAAGGG GTTGTGGTCG GGGAGCTGGG  
1351 GTACAGGTT GGGAGGGG AAGAGAAATT TTTATTTTG AACCCCTGTG  
1401 TCCCTTTTGC ATAAGATTAA AGGAAGGAAA AGT

Figure 1(ii)

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**Figure 2**  
Substitute Sheet  
(Rule 26) RO/AU

5/65

1	CTCAGCGCCC	AGCCGCTTCC	TGCCTGGATT	CCACAGCTTC	GCGCCGTGTA
51	CTGTGCCCC	ATCCCTGCGC	GCCAGCCTG	CCAAGCAGCG	TGCCCCGGTT
101	GCAGGCGTCA	TGCAGCGGGC	GCGACCCACG	CTCTGGGCCG	CTGCGCTGAC
151	TCTGCTGGTG	CTGCTCCGCG	GGCCGCCGGT	GGCGCGGGCT	GGCGCGAGCT
201	CGGGGGGCTT	GGTCCCCTG	GTGCGCTGCG	AGCCGTGCGA	CGCGCGTGCA
251	CTGGCCCCAGT	GCGCGCCTCC	GCCCGCCGTG	TGCGCGGAGC	TGGTGCGCCA
301	GCCGGGCTGC	GGTGCTGCC	TGACGTGCGC	ACTGAGCGAG	GCCAGCCCGT
351	GCGGCATCTA	CACCGAGCGC	TGTGGCTCCG	GCCTTCGCTG	CCAGCCGTCG
401	CCCGACGAGG	GCGACCGCT	GCAGGCGCTG	CTGGACGGCC	GCGGGCTCTG
451	CGTCAACGCT	AGTGCCGTCA	GCCGCCCTGCG	CGCCTACCTG	CTGCCAGCGC
501	CGCCAGCTCC	AGGAAATGCT	AGTGAGTCGG	AGGAAGACCG	CAGCGCCGGC
551	AGTGTGGAGA	GCCCGTCCGT	CTCCAGCACG	CACCGGGTGT	CTGATCCCAA
601	GTTCCACCCC	CTCCATTCAA	AGATAATCAT	CATCAAGAAA	GGGCATGCTA
651	AAGACAGCCA	GCGTACAAA	GTTGACTACG	AGTCTCAGAG	CACAGATACC
701	CAGAACTTCT	CCTCCGAGTC	CAAGCGGGAG	ACAGAATATG	GTCCCTGCCG

Figure 2(i)



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751 TAGAGAAATG GAAGACACAC TGAATCACCT GAAGTTCCTC AATGTGCTGA  
801 GTCCACAGGG TGTACACATT CCCAACTGTG ACAAGAAGGG ATTTTATAAG  
851 AAAAAGCAGT GTCGCCCTTC CAAAGGCAGG AAGCGGGGCT TCTGCTGGTG  
901 TGTGGATAAG TATGGGCAGC CTCTCCAGG CTACACCACC AAGGGGAAGG  
951 AGGACGTGCA CTGCTACAGC ATGCAGAGCA AGTAGACGCC TGCCGCAAGT  
1001 TAATGTGGAG CTCAAATATG CCTTATTTTG CACAAAAGAC TGCCAAGGAC  
1051 ATGACCAGCA GCTGGCTACA GCCTCGATTG ATATTTCTGT TTGTGGTGAA  
1101 CTGATTTTTT TTAACCAAA GTTAGAAAG AGGTTTTTGA AATGCCATAG  
1151 GTTTCCTTGA ATGGTAAACT TGAGCATCTT TTCACTTTCC AGTAGTCAGC  
1201 AAAGAGCAGT TTGAATTTTC TTGTCGCTTC CTATCAAAAT ATTCAGAGAC  
1251 TCGAGCACAG CACCCAGACT TCATGCGCCC GTGGAATGCT CACCACATGT  
1301 TGGTCGAAGC GGCCGACCAC TGACTTTGTG ACTTAGGCGG CTGTGTTGCC  
1351 TATGTAGAGA ACACGCTTCA CCCCACCTCC CCGTACAGTG CGCACAGGCT  
1401 TTATCGAGAA TAGGAAAACC TTTAAACCCC GTCATCCGG ACATCCCAAC  
1451 GCATGCTCCT GGAGCTCACA GCCTTCTGTG GTGTCATTTC TGAAACAAGG

Figure 2(ii)

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1501 GCGTGGATCC CTCACCAAG AAGAA TGTTT ATGTCTTCAA GTGACCTGTA  
1551 CTGCTTGGG ACTATTGGAG AAAATAAGGT GGAGTCCTAC TTGTTTAAAA  
1601 AATATGTATC TAAGAAATGTT CTAGGGCACT CTGGGAACCT ATAAAGGCAG  
1651 GTATTTTCGG CCTCCTCTT CAGGAATCTT CCTGAAGACA TGGCCCAGTC  
1701 GAAGGCCAG GATGGCTTTT GCTGGGGCC CGTGGGGTAG GAGGACAGA  
1751 GAGACGGGAG AGTCAGCCTC CACATTCAGA GGCATCACAA GTAATGGCAC  
1801 AATTCTTCGG ATGACTGCAG AAAATAGTGT TTTGTAGTTC AACAACTCAA  
1851 GACGAAGCTT ATTTCTGAGG ATAAGCTCTT TAAAGGCAAA GCTTTATTTT  
1901 CATCTCTCAT CTTTGTCTCCT CCTTAGCACA ATGTAAAAAA GAATAGTAAT  
1951 ATCAGAACAG GAAGGAGGAA TGGCTTGCTG GGGAGCCCAT CCAGGACACT  
2001 GGGAGCACAT AGAGATTCAC CCATGTTTGT TGAACCTAGA GTCATTCTCA  
2051 TGCTTTTCTT TATAATTCAC ACATATATGC AGAGAAGATA TGTCTTGT  
2101 AACATTGTAT ACAACATAGC CCCAAATATA GTAAGATCTA TACTAGATAA  
2151 TCCTAGATGA AATGTTAGAG ATGCTATATG ATACAACCTGT GGCCATGACT  
2201 GAGGAAAGGA GCTCACGCCC AGAGACTGGG CTGCTCTCCC GGAGGCCAAA

Figure 2(iii)

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2251	CCCAAGAAGG	TCTGGCAAAG	TCAGGCTCAG	GGAGACTCTG	CCCTGCTGCA
2301	GACCTCGGTG	TGGACACACG	CTGCATAGAG	CTCTCCTTGA	AAACAGAGGG
2351	GTCTCAAGAC	ATTCTGCCCTA	CCTATTAGCT	TTTCTTTTATT	TTTTTAACTT
2401	TTTGGGGGGA	AAAGTATTTT	TGAGAAGTTT	GTCTTGCAAT	GTATTTATAA
2451	ATAGTAAATA	AAGTTTTTAC	CATT		

Figure 2(iv)

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(i)
(ii)
(iii)
(iv)
(v)
(vi)
(vii)

Figure 3

1	TTTTTTTTTT	TTTGTGAGAAA	GGGAATTTC	TCCCAAATAA	AAGGAATGAA
51	GTCTGGCTCC	GGAGGAGGGT	CCCCGACCTC	GCTGTGGGG	CTCCTGTTTC
101	TCTCCGCCGC	GCTCTCGCTC	TGGCCGACGA	GTGAGAAAT	CTGCGGGCCA
151	GGCATCGACA	TCCGCAACGA	CTATCAGCAG	CTGAAGCGCC	TGGAGAACTG
201	CACGGTGATC	GAGGGCTACC	TCCACATCCT	GCTCATCTCC	AAGGCCGAGG
251	ACTACCGCAG	CTACCGCTTC	CCAAGCTCA	CGGTCATTAC	CGAGTACTTG
301	CTGCTGTTCC	GAGTGGCTGG	CCTCGAGAGC	CTCGGAGACC	TCTTCCCCAA
351	CCTCACGGTC	ATCCGCGGCT	GGAAACTCTT	CTACAACACTAC	GCCCTGGTCA
401	TCTTCGAGAT	GACCAATCTC	AAGGATATTG	GGCTTTACAA	CCTGAGGAAC
451	ATTACTCGGG	GGGCCATCAG	GATTGAGAAA	AATGCTGACC	TCTGTTACCT
501	CTCCACTGTG	GACTGGTCCC	TGATCCTGGA	TGCGGTGTCC	AATAACTACA
551	TTGTGGGGAA	TAAGCCCCCA	AAGGAATGTG	GGGACCTGTG	TCCAGGGACC
601	ATGGAGGAGA	AGCCGATGTG	TGAGAAGACC	ACCATCAACA	ATGAGTACAA
651	CTACCGCTGC	TGGACCAACA	ACCGCTGCCA	GAAAATGTGC	CCAAGCACGT
701	GTGGGAAGCG	GGCGTGCACC	GAGAACAAATG	AGTGCTGCCA	CCCCGAGTGC

Figure 3(i)

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751 CTGGGCAGCT GCAGCGCGCC TGACAAACGAC ACGGCCCTGTG TAGCTTGCCG  
801 CCACTACTAC TATGCCCGGTG TCTGTGTGCC TGCCTGCCCCG CCCAACACCT  
851 ACAGGTTTGA GGGCTGGCGC TGTGTGGACC GTGACTTCTG CGCCAACATC  
901 CTCAGCGCCG AGAGCAGCGA CTCGAGGGG TTTGTGATCC ACGACGGCGA  
951 GTGCATGCAG GAGTGCCCTT CCGGCTTCAT CCGCAACGGC AGCCAGAGCA  
1001 TGTA CTGCAT CCCTTGTGAA GGTCCCTTGCC CGAAGGTCTG TGAGGAAGAA  
1051 AAGAAACAA AGACCATGA TTCTGTTACT TCTGCTCAGA TGCTCCAAGG  
1101 ATGCACCATC TTCAAGGGCA ATTTGCTCAT TAACATCCGA CGGGGAATA  
1151 ACATTGCTTC AGAGCTGGAG AACTTCATGG GGCTCATCGA GGTGGTGACG  
1201 GGCTACGTGA AGATCCGCCA TTCTCATGCC TTGGTCTCCT TGTCCCTTCT  
1251 AAAA AACCTT CGCCTCATCC TAGGAGAGGA GCAGCTAGAA GGAATTACT  
1301 CCTTCTACGT CCTCGACAAC CAGAACTGC AGCAACTGTG GGACTGGGAC  
1351 CACCGCAACC TGACCATCAA AGCAGGGAAA ATGTACTTTG CTTTCAATCC  
1401 CAAATTATGT GTTCCGAAA TTTACCGCAT GGAGGAAGTG ACGGGGACTA  
1451 AAGGGCGCCA AAGCAAAGGG GACATAAACA CCAGGAACAA CGGGGAGAGA

Figure 3(ii)

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1501 GCCTCCTGTG AAAGTGACGT CCTGCATTTC ACCTCCACCA CCACGTCGAA  
1551 GAATCGCATC ATCATAACCT GGCACCGGTA CCGGCCCCCT GACTACAGGG  
1601 ATCTCATCAG CTTCAACCGTT TACTACAAGG AAGCACCCCT TAAGAATGTC  
1651 ACAGAGTATG ATGGGCAGGA TGCCCTGCGGC TCCAACAGCT GGAACATGGT  
1701 GGACGTGGAC CTCCCGCCCA ACAAGGACGT GGAGCCCGGC ATCTTACTAC  
1751 ATGGGCTGAA GCCCTGGACT CAGTACGCCG TTTACGTCAA GGCTGTGACC  
1801 CTCACCATGG TGGAGAACGA CCATATCCGT GGGGCCAAGA GTGAGATCTT  
1851 GTACATTTCG ACCAATGCTT CAGTTCCTTC CATTCCTTG GACGTTCTTT  
1901 CAGCATCGAA CTCCTCTTCT CAGTTAATCG TGAAGTGGAA CCCTCCCTCT  
1951 CTGCCCCAAG GCAACCTGAG TTAATACTT GTGCGCTGGC AGCGGCAGCC  
2001 TCAGGACGGC TACCTTTACC GGCACAATTA CTGCTCCAAA GACAAAATCC  
2051 CCATCAGGAA GTATGCCGAC GGCACCATCG ACATTGAGGA GGTACACAGAG  
2101 AACCCCAAGA CTGAGGTGTG TGGTGGGGAG AAAGGGCCTT GCTGCGCCTG  
2151 CCCCAAAACT GAAGCCGAGA AGCAGGCCGA GAAGGAGGAG GCTGAATACC  
2201 GCAAAGTCTT TGAGAATTTC CTGCACAACT CCATCTTCGT GCCCAGACCT

Figure 3(iii)

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2251 GAAAGGAAGC GGAGAGATGT CATGCAAGTG GCCAACACCA CCATGTCCAG  
2301 CCGAAGCAGG AACACCACGG CCGCAGACAC CTACAACATC ACCGACCCGG  
2351 AAGAGCTGGA GACAGAGTAC CCTTCTTTG AGAGCAGAGT GGATAACAAG  
2401 GAGAGAACTG TCATTCTAA CCTTCGGCCT TTCACATTGT ACCGCATCGA  
2451 TATCCACAGC TGCAACCACG AGGCTGAGAA GCTGGGCTGC AGCGCCTCCA  
2501 ACTTCGTCTT TGCAAGGACT ATGCCCGCAG AAGGAGCAGA TGACATTCCCT  
2551 GGGCCAGTGA CCTGGGAGCC AAGGCCCTGAA AACTCCATCT TTTTAAAGTG  
2601 GCCGGAACCT GAGAAATCCCA ATGGATTGAT TCTAATGTAT GAAATAAAAT  
2651 ACGGATCACA AGTTGAGGAT CAGCGAGAAT GTGTGTCCAG ACAGGAATAC  
2701 AGGAAGTATG GAGGGGCCAA GCTAAACCCGG CTAAACCCGG GGAACCTACAC  
2751 AGCCCGGATT CAGGCCACAT CTCTCTCTGG GAATGGGTCG TGGACAGATC  
2801 CTGTGTTCTT CTATGTCCAG GCCAAACACG GATATGAAA CTTCATCCAT  
2851 CTGATCATCG CTCGTGCCGT CGCTGTCCCTG TTGATCGTGG GAGGGTTGGT  
2901 GATTATGCTG TACGTCTTCC ATAGAAAGAG AAATAACAGC AGGCTGGGGA  
2951 ATGGAGTGCT GTATGCCTCT GTGAACCCGG AGTACTTCAG CGCTGCTGAT

Figure 3(iv)



14/65

3001 GTGTACGTTC CTGATGAGTG GGAGGTGGCT CGGAGAAGA TCACCATGAG  
3051 CCGGGAAC TT GGCAGGGGT CGTTGGGAT GGCTATGAA GGAGTTGCCA  
3101 AGGGTGTGGT GAAAGATGAA CCTGAAACCA GAGTGGCCAT TAAACACAGTG  
3151 AACGAGGCCG CAAGCATGCG TGAGAGGATT GAGTTTCTCA ACGAAGCTTC  
3201 TGTGATGAAG GAGTTCAATT GTCACCATGT GTGCGGATTG CTGGGTGTGG  
3251 TGTCCCAAGG CCAGCCAACA CTGGTCATCA TGGAAC TGAT GACACGGGCG  
3301 GATCTCAAAA GTTATCTCCG GTCTCTGAGG CCAGAAATGG AGAATAATCC  
3351 AGTCCTAGCA CCTCCAAGCC TGAGCAAGAT GATTCAGATG GCCGGAGAGA  
3401 TTGCAGACGG CATGGCATACTCAACGCCA ATAAGTTCTG CCACAGAGAC  
3451 CTTGCTGCCC GGAATTGCAT GTAGCCGAA GATTTCACAG TCAAAATCGG  
3501 AGATTTTGGT ATGACGCGAG ATATCTATGA GACAGACTAT TACCGGAAAG  
3551 GAGGCAAAGG GCTGCTGCCC GTGCGCTGGA TGTCTCCTGA GTCCCTCAAG  
3601 GATGGAGTCT TCACCACTTA CTCGGACGTC TGGTCTTTCG GGGTCGTCCT  
3651 CTGGGAGATC GCCACACTGG CCGAGCAGCC CTACCAGGCG TTGTCCAACG  
3701 AGCAAGTCCT TCGCTTCGTC ATGGAGGGCG GCCTTCTGGA CAAGCCAGAC

Figure 3(v)

15/65

3751 AACTGTCCCTG ACATGCTGTT TGAAGTATG CGCATGTGCT GGCAGTATAA  
3801 CCCCAAGATG AGGCCCTTCCT TCCTGGAGAT CATCAGCAGC ATCAAAGAGG  
3851 AGATGGAGCC TGGCTTCCGG GAGGTCTCCT TCTACTACAG CGAGGAGAAC  
3901 AAGCTGCCCG AGCCGGAGGA GCTGGACCTG GAGCCAGAGA ACATGGAGAG  
3951 CGTCCCCCTG GACCCCTCGG CCTCCTCGTC CTCCCTGCCA CTGCCCGACA  
4001 GACACTCAGG ACACAAGGCC GAGAACGGCC CCGGCCCTGG GGTGCTGGTC  
4051 CTCCGCGCCA GCTTCGACGA GAGACAGCCT TACGCCACCA TGAACGGGGG  
4101 CCGCAAGAAC GAGCGGGCCT TGCCGCTGCC CCAGTCTTCG ACCTGCTGAT  
4151 CCTTGGATCC TGAATCTGTG CAAACAGTAA CGTGTGCGCA CGCGCAGCGG  
4201 GGTGGGGGGG GAGAGAGAGT TTTAACAAATC CATTACAAG CCTCCTGTAC  
4251 CTCAGTGGAT CTTCAGTTCT GCCCTTGCTG CCCGCGGAG ACAGCTTCTC  
4301 TGCAGTAAAA CACATTTGGG ATGTTCCCTTT TTTCAATATG CAAGCAGCTT  
4351 TTTATTCCCT GCCCAAACCC TTAAGTACA TGGGCCCTTA AGAACCTTAA  
4401 TGACAACACT TAATAGCAAC AGAGCACTTG AGAACAGTC TCCTCACTCT  
4451 GTCCCTGTCC TTCCCTGTTC TCCCTTTCTC TCTCCTCTCT GCTTCATAAC

Figure 3(vi)

16/65

4501 GGAAAAATAA TTGCCACAAG TCCAGCTGGG AAGCCCTTTT TATCAGTTTG  
4551 AGGAAGTGGC TGTCCCTGTG GCCCCATCCA ACCACTGTAC ACACCCGCCT  
4601 GACACCGTGG GTCATTACAA AAAACACCGT GGAGATGGAA ATTTTACCT  
4651 TTATCTTTCA CCTTCTTAGG GACATGAAAT TTACAAAGGG CCATCGTTCA  
4701 TCCAAGGCTG TTACCATTTT AACGCTGCCT AATTTGCCA AAATCCTGAA  
4751 CTTTCTCCCT CATCGGCCCG GCGCTGATTC CTCGTGTCCG GAGGCATGGG  
4801 TGAGCATGGC AGCTGGTTGC TCCATTGAG AGACACGCTG GCGACACACT  
4851 CCGTCCATCC GACTGCCCCCT GCTGTGCTGC TCAAGGCCAC AGGCACACAG  
4901 GTCTCATTGC TTCTGACTAG ATTATTATT GGGGGAAC TG GACACAATAG  
4951 GTCTTTCTCT CAGTGAAGGT GGGGAGAAGC TGAACCGGC

Figure 3 (vii)

17/65



Figure 4a

18/65

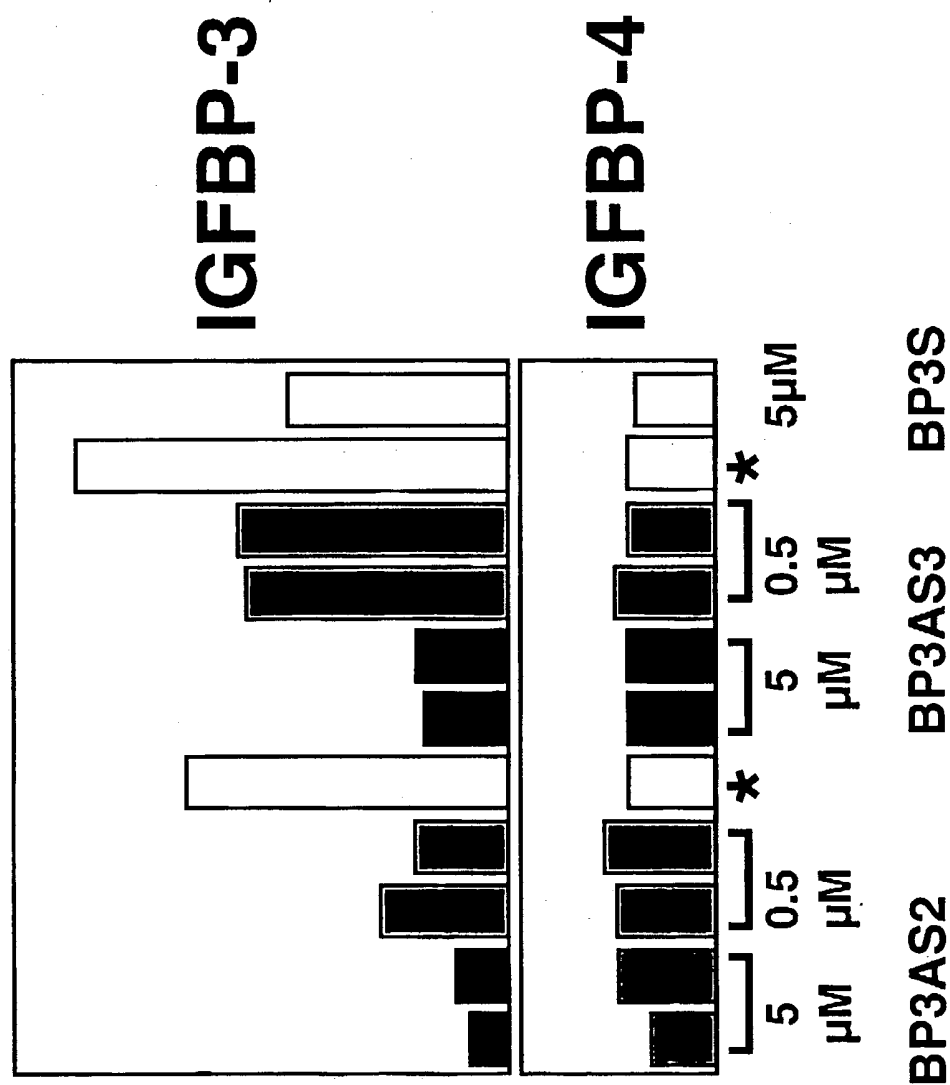


Figure 4b

19/65

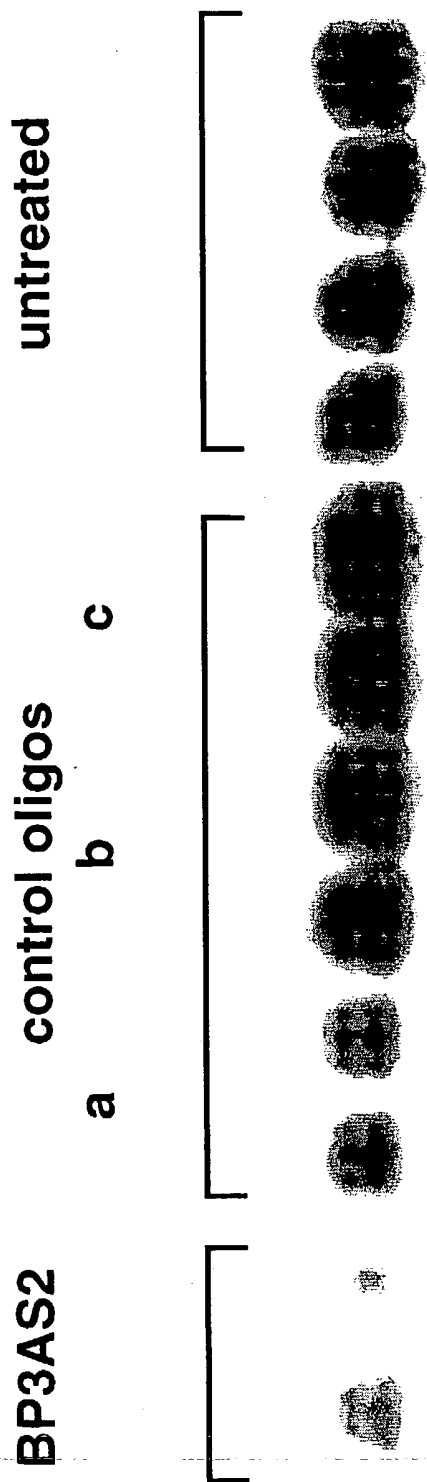


Figure 5a

20/65

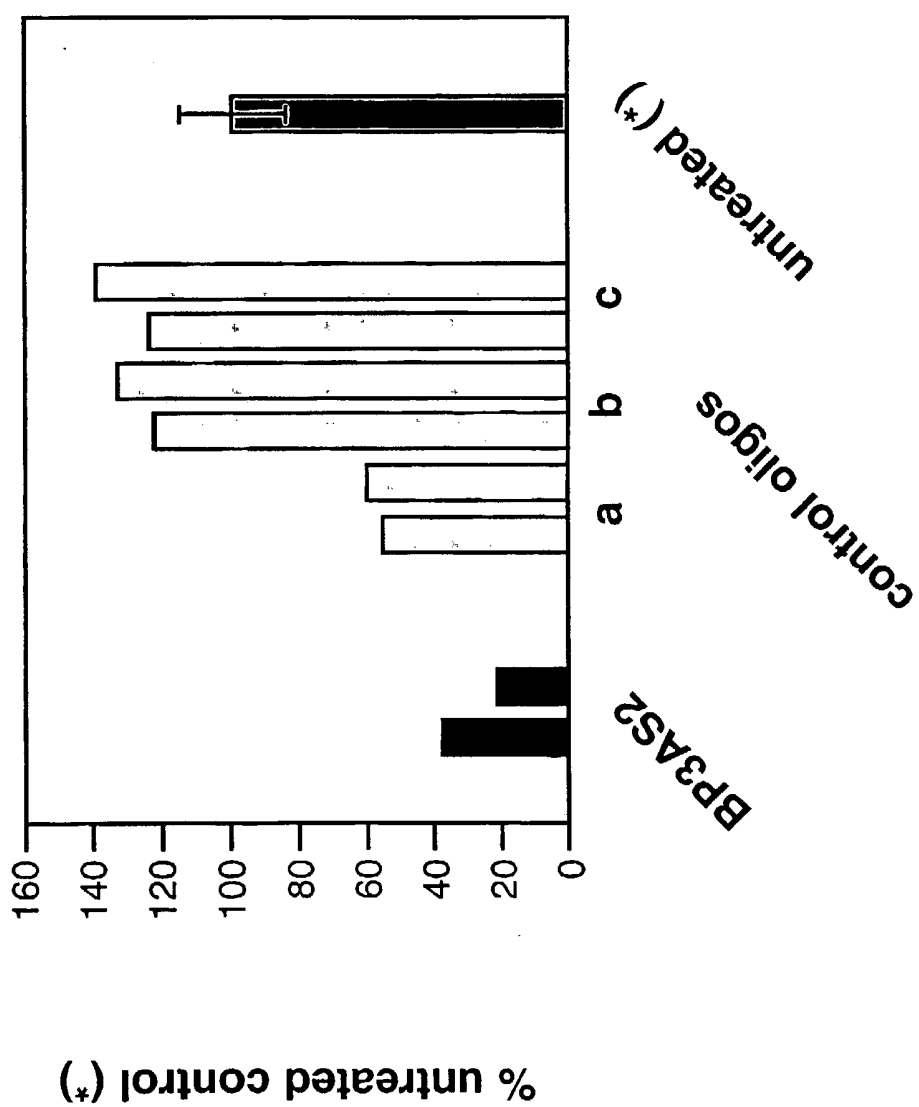


Figure 5b

21/65

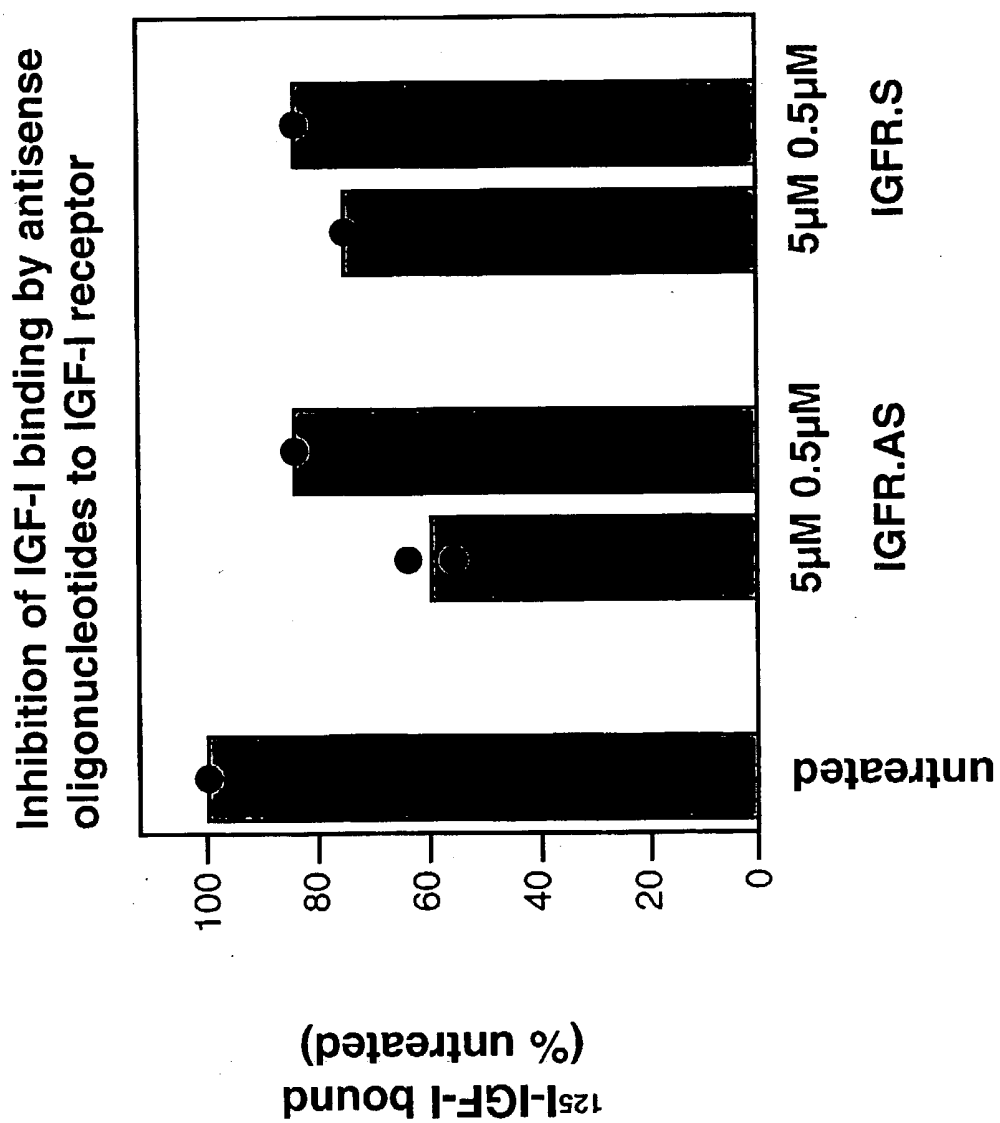


Figure 6

Substitute Sheet  
(Rule 26) RO/AU



22/65

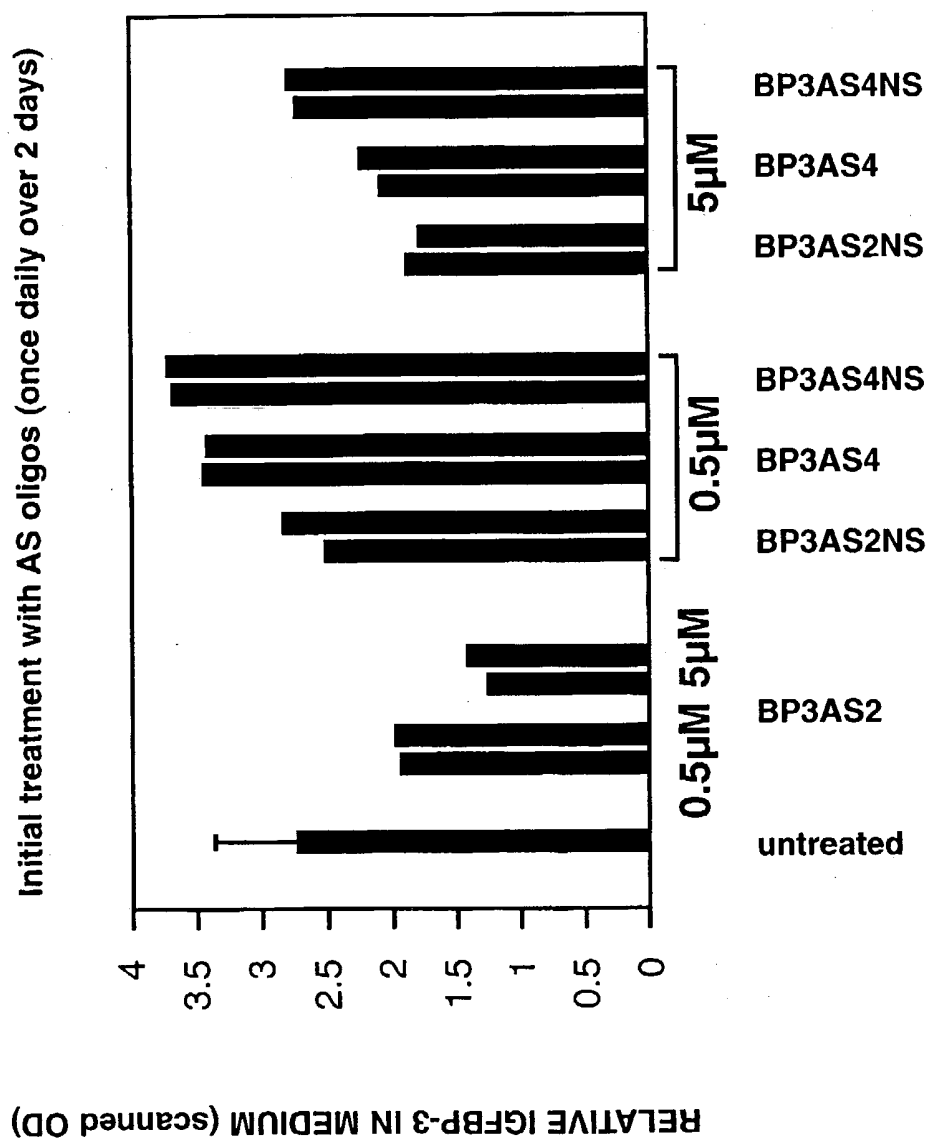


Figure 7

Substitute Sheet  
(Rule 26) RO/AU

23/65

## Optimization of IGFBP-3 AS oligo concentration

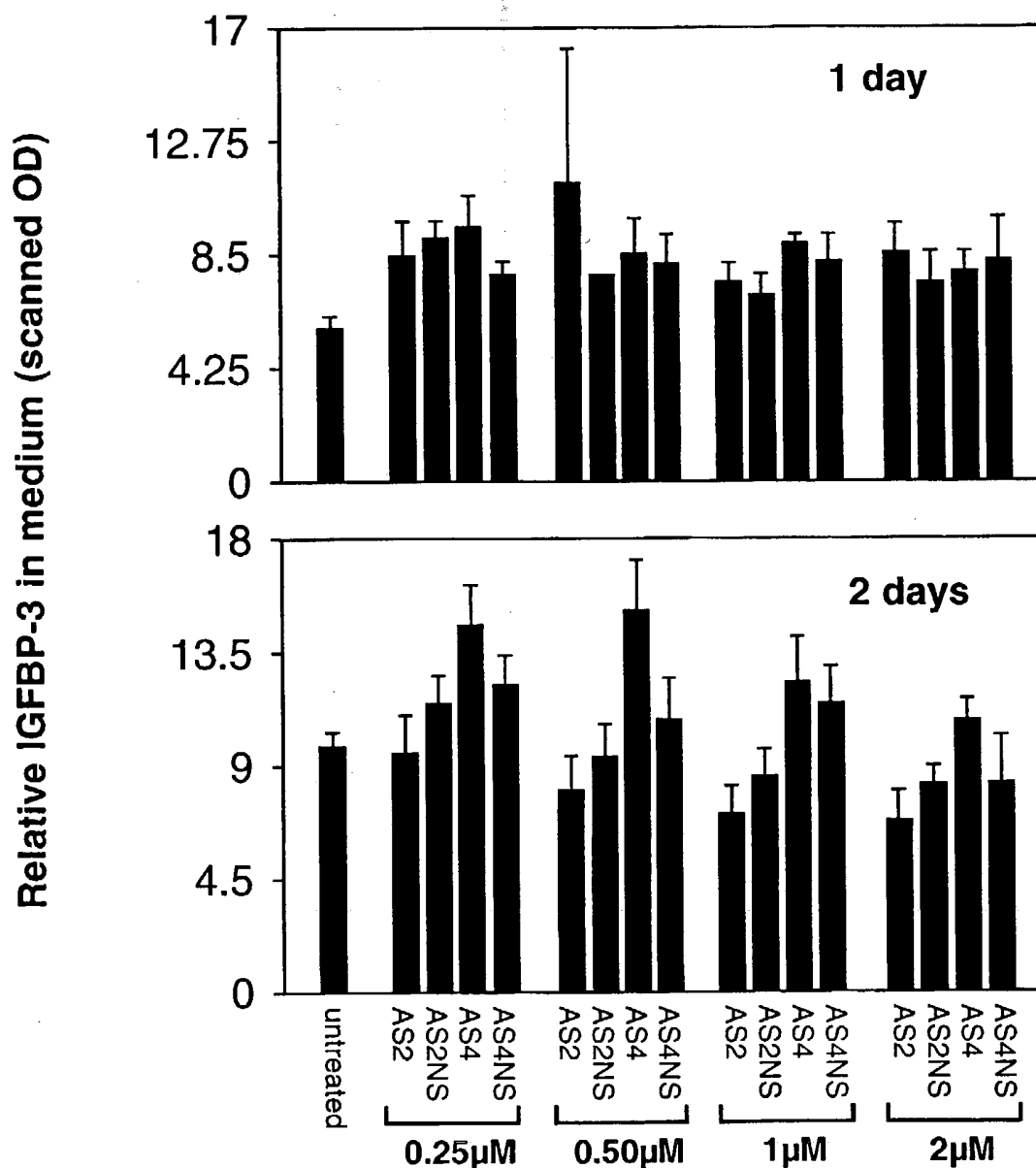
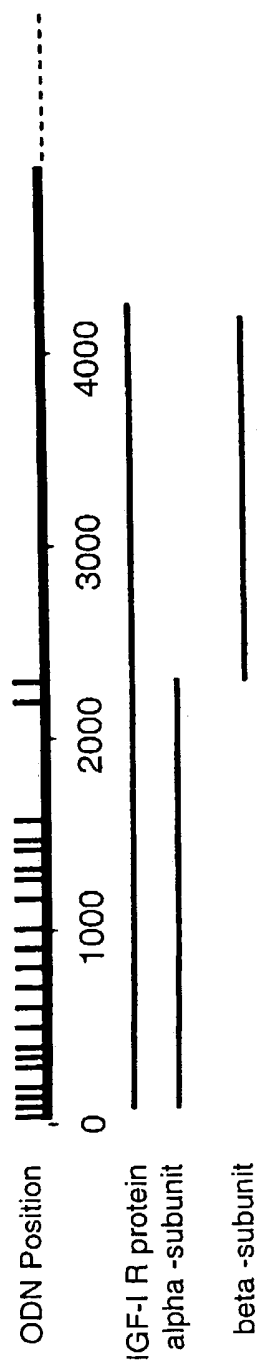


Figure 8

Substitute Sheet  
(Rule 26) RO/AU

24/65

# Map of IGF-I Receptor mRNA and position of target ODNs

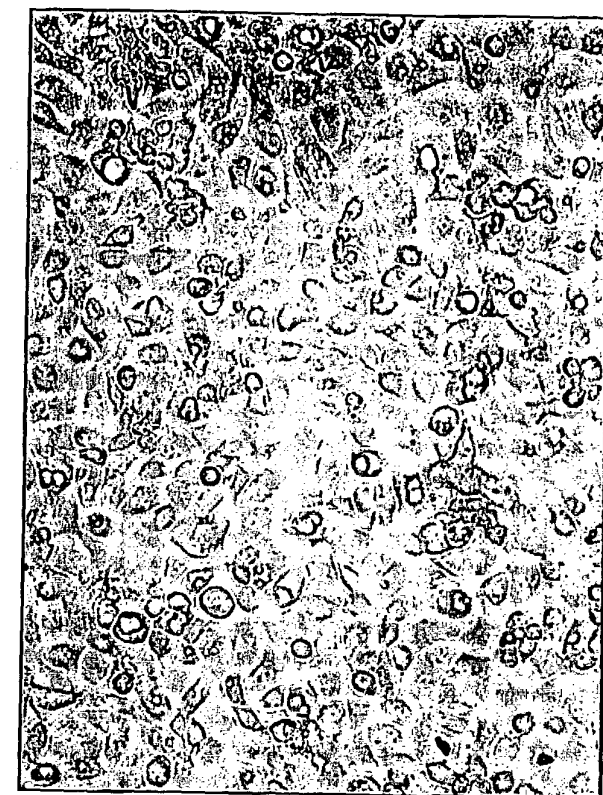


- Position of the 21 tested ODNs ( | )
- mRNA transcript lengths = 7Kb and 11Kb
- coding sequence 46-4149

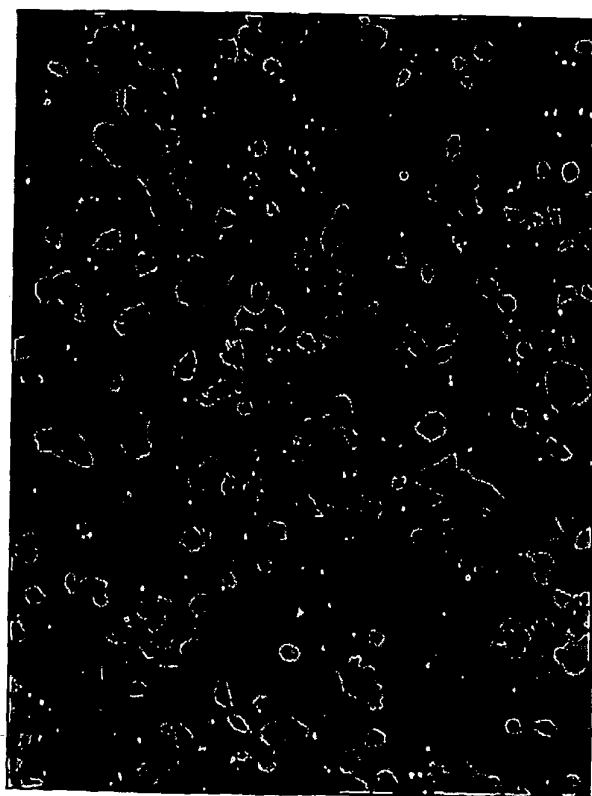
Figure 9

25/65

Lipid-mediated uptake of oligonucleotide in keratinocytes



B



A

Figure 10

26/65

# **Uptake (A) and toxicity (B) of ODN/ lipid complexes in keratinocytes**

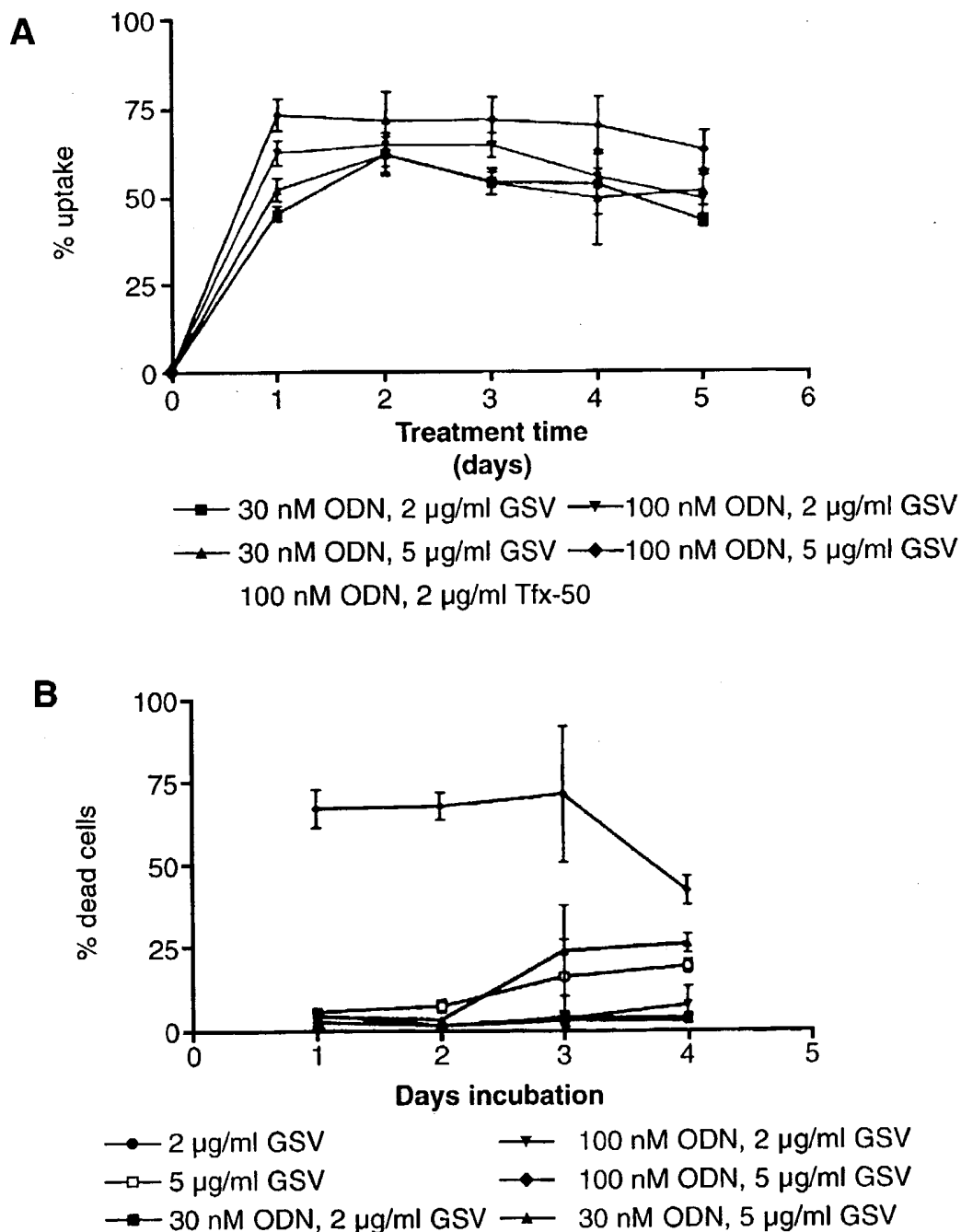


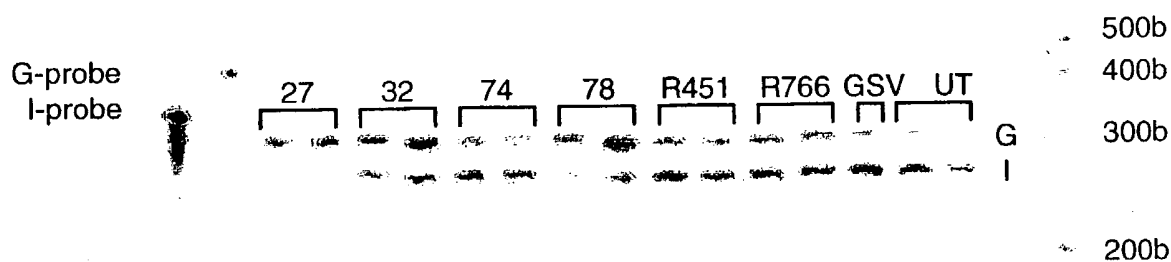
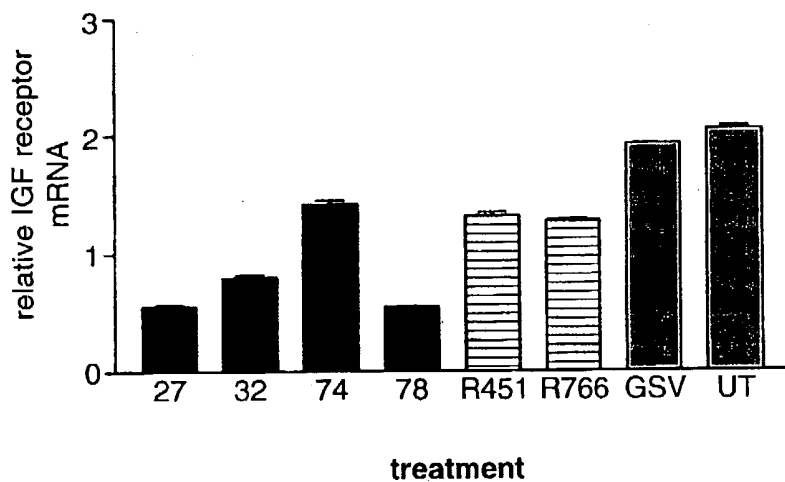
Figure 11

Substitute Sheet  
(Rule 26) RO/AU

1/3/05, EAST Version: 2.0.1.4

27/65

**IGF-I Receptor mRNA in ODN  
treated (30nM) HaCaT cells (2µg/ml GSV)**

**A****B****Figure 12**

Substitute Sheet  
(Rule 26) RO/AU

28/65

IGF-I receptor mRNA in ODN treated (30nM)  
HaCaT cells (2µg/ml GSV)

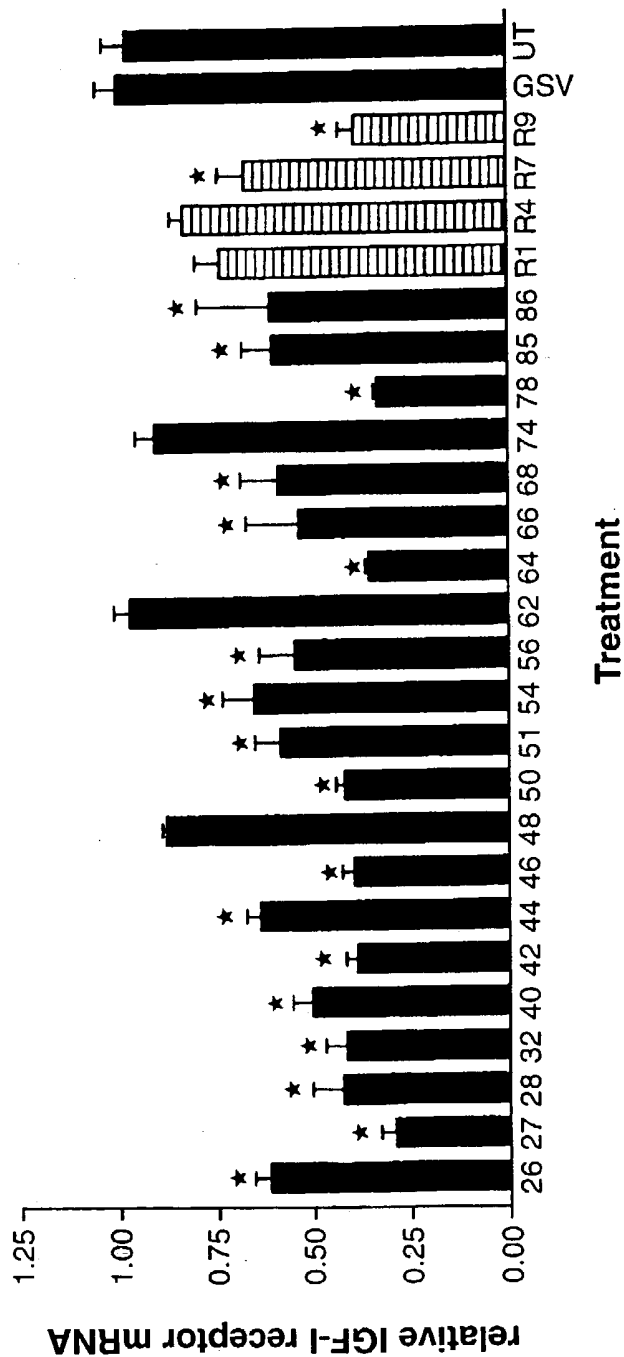
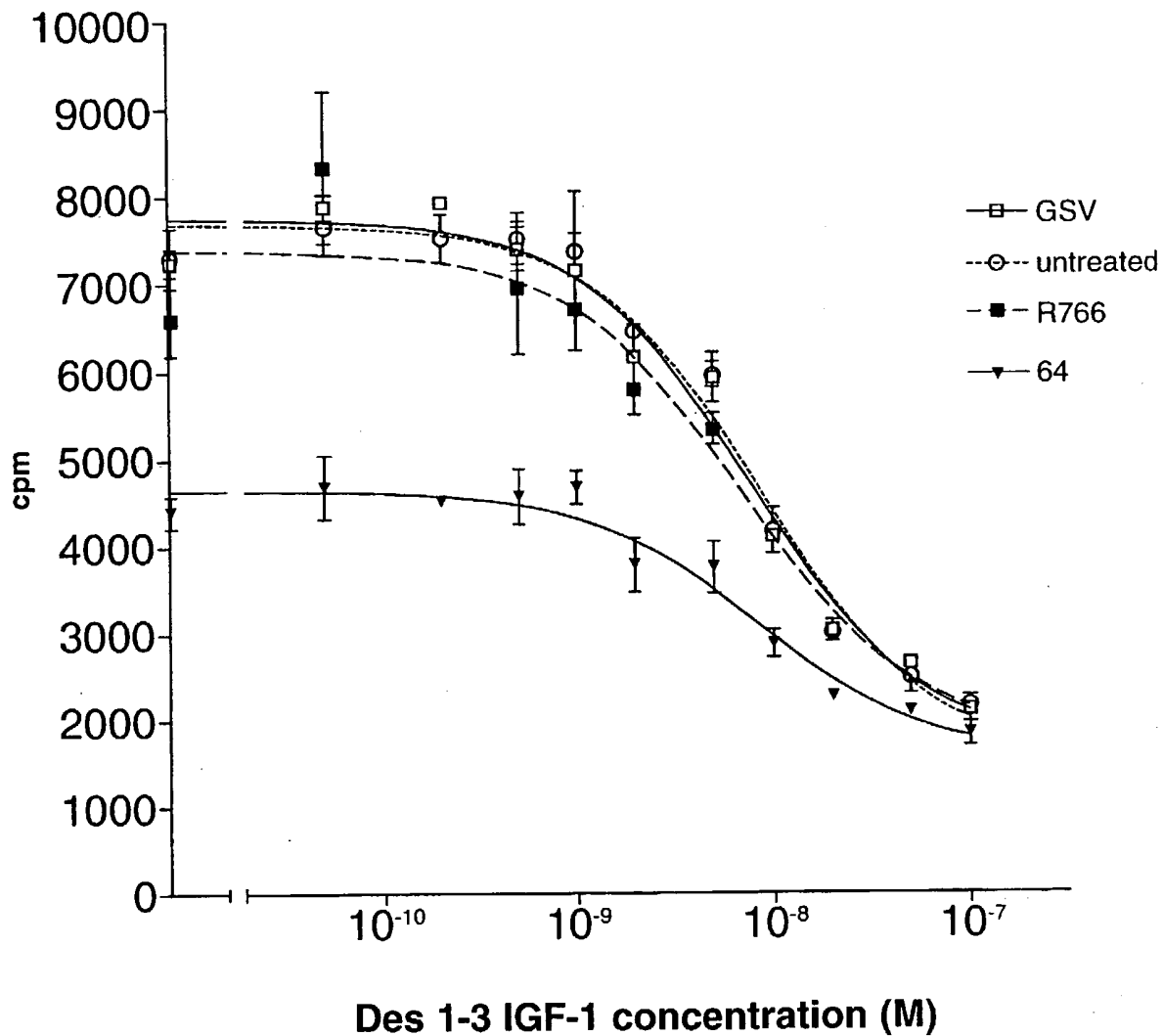


Figure 13

29/65

**Effect of antisense oligonucleotides on IGF-1  
receptor levels on the surface of keratinocytes:**  
Competition Assay -  $^{125}$ I IGF-1 vs Des 1-3 IGF-1



**Figure 14**  
Substitute Sheet  
(Rule 26) RO/AU



30/65

**Effect of antisense oligonucleotides on IGF-1  
receptor levels on the surface of keratinocytes:**  
Competition Assay -  $^{125}$ I IGF-1 vs Des 1-3 IGF-1

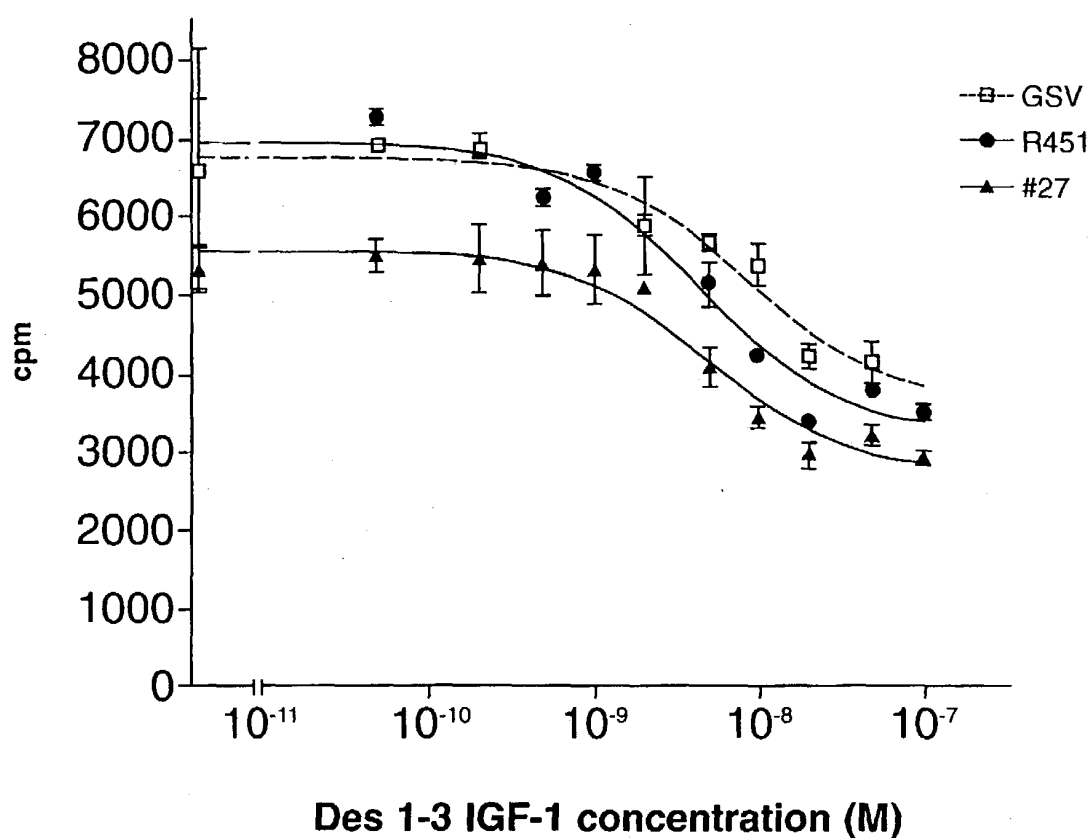


Figure 15

Substitute Sheet  
(Rule 26) RO/AU

31/65

H&E stained sections of (A) psoriatic skin biopsy prior to grafting and  
(B) 49 day old psoriatic skin graft using skin from same donor

**A****B**

Figure 16

Substitute Sheet  
(Rule 26) RO/AU

32/65

Uptake of oligonucleotide after intradermal injection  
into psoriatic skin graft on a nude mouse

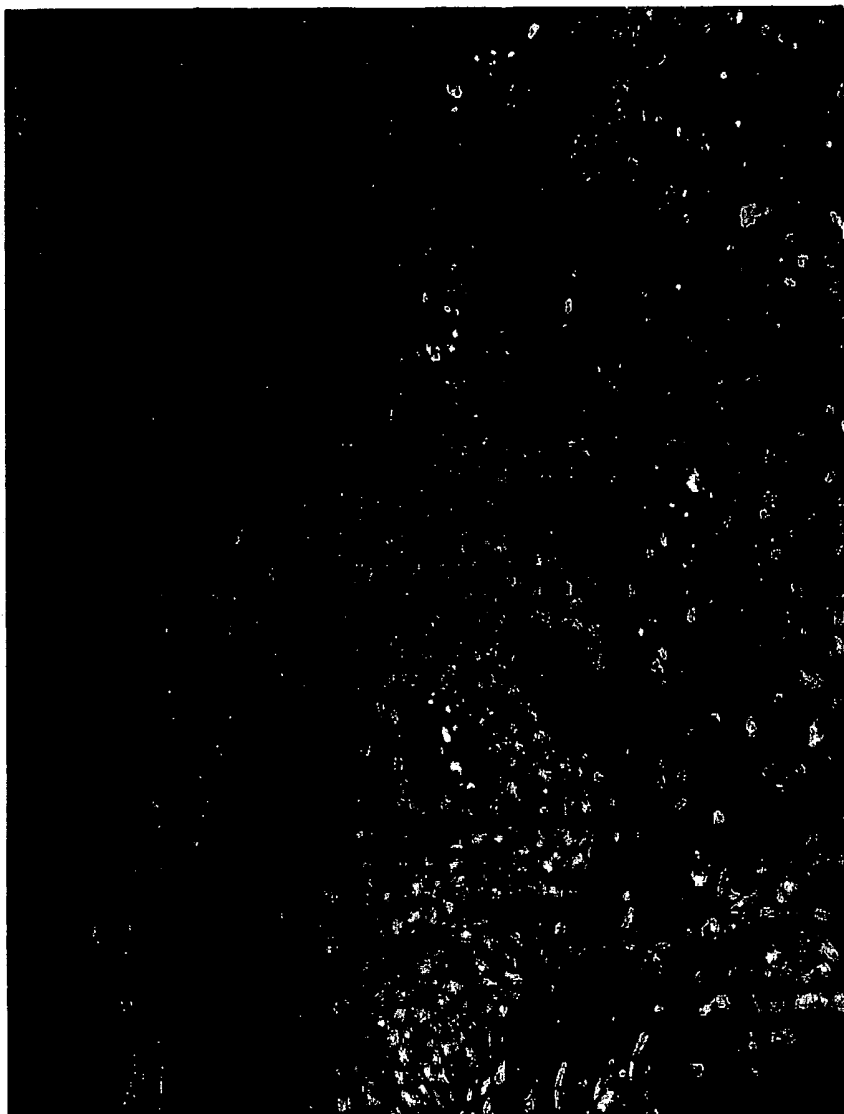
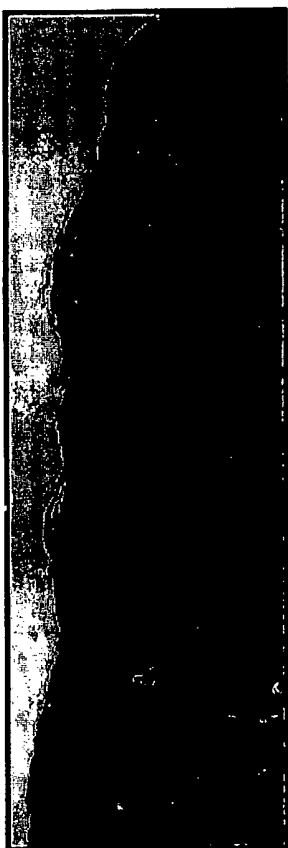


Figure 17

Substitute Sheet  
(Rule 26) RO/AU

33/65

Pregraft, Donor JH



Donor JH, PBS treated (50  $\mu$ l)



Donor JH, #50 treated (50  $\mu$ l, 10  $\mu$ M)

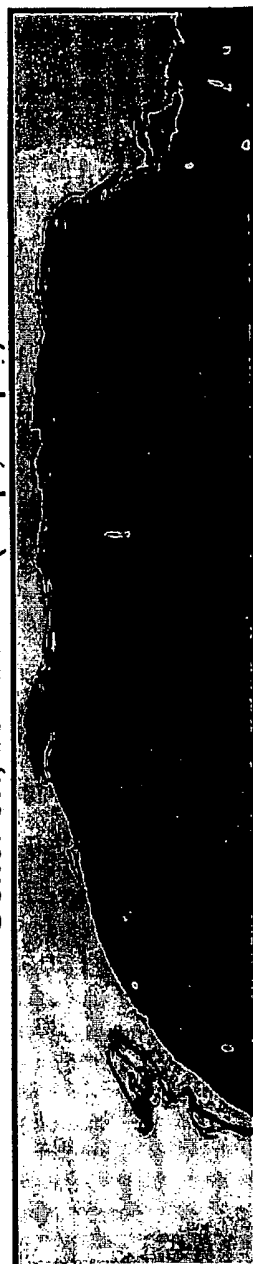


Figure 18a

34/65

Donor LB, pregraft



Donor LB, PBS treated (50  $\mu$ l)



Donor LB, #74 treated (50  $\mu$ l, 10  $\mu$ M)

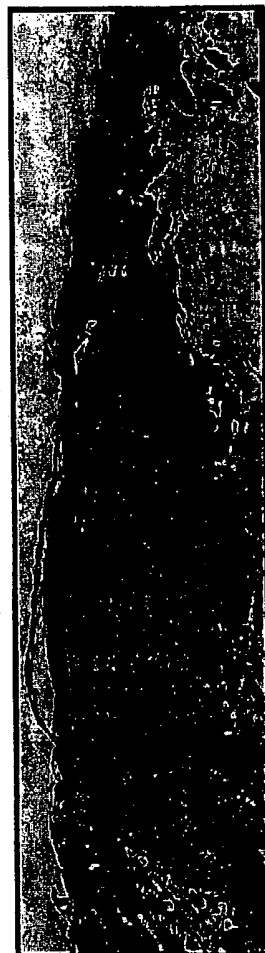


Figure 18b

Substitute Sheet  
(Rule 26) RO/AU

35/65

Donor PW, pregraft



Donor PW, R451 treated (50  $\mu$ l, 10 $\mu$ M)



Donor LB, #74 treated (50  $\mu$ l, 10  $\mu$ M)



Figure 18c

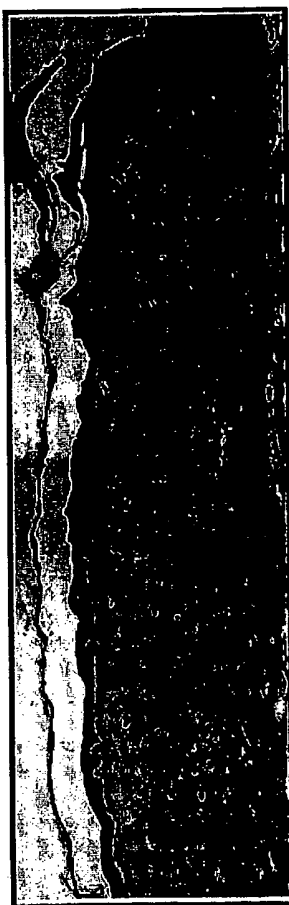
Substitute Sheet  
(Rule 26) RO/AU

36/65

Donor GM, pregraft



Donor GM, R451 treated (50  $\mu$ l, 10  $\mu$ M)



Donor GM, #27 treated (50  $\mu$ l, 10  $\mu$ M)

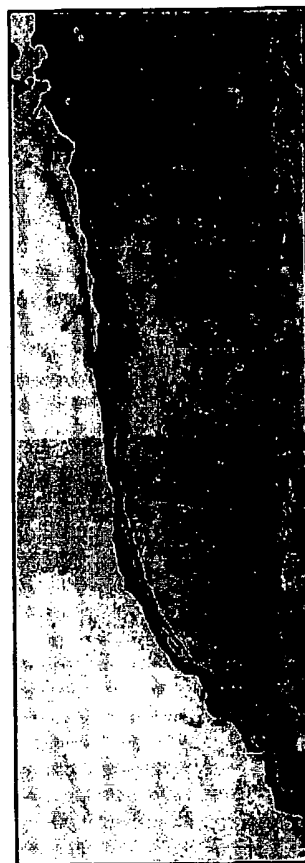


Figure 18d

Substitute Sheet  
(Rule 26) RO/AU

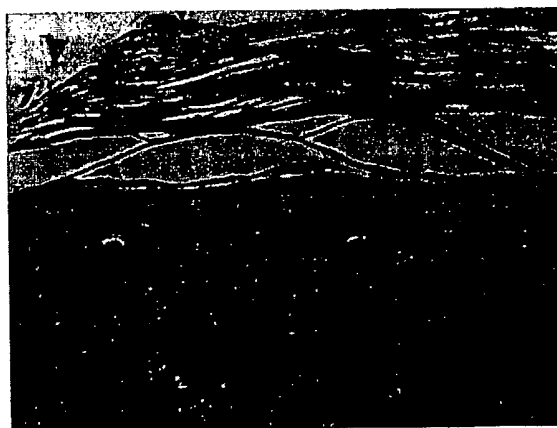
37/65



**Donor JH Pregraft**



**Donor JH PBS treated 50ul**



**Donor JH # 50 treated 50ul, 10uM**

**Figure 19a**

Substitute Sheet  
(Rule 26) RO/AU



38/65



**Donor LB Pregraft**



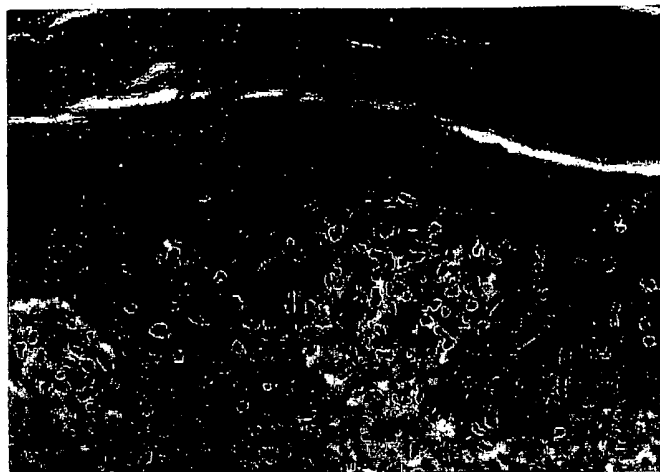
**Donor LB PBS treated 50ul**



**Donor LB # 74 treated 50ul, 10uM**

**Figure 19b**

39/65



Donor PW Pregraft



Donor PW R451 treated 50ul, 10um



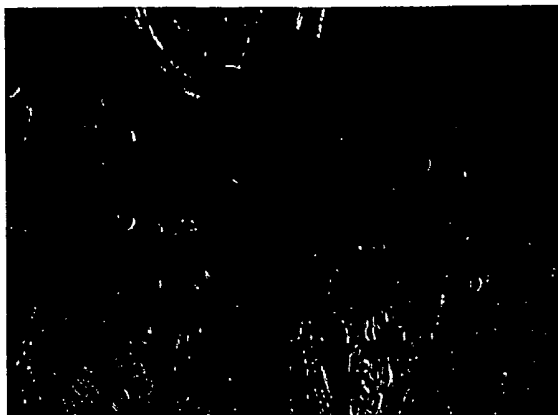
Donor PW # 74 treated 50ul, 10uM

Figure 19c

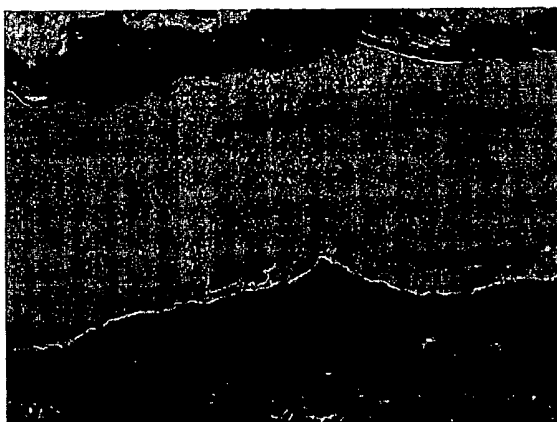
Substitute Sheet

1/3/05, EAST Version: 2.0.1.4

40/65



**Donor GM Pregraft**



**Donor GM R451 treated 50ul, 10um**



**Donor GM # 27 treated 50ul, 10uM**

**Figure 19d**

Substitute Sheet  
(Rule 26) RO/AU

1/3/05, EAST Version: 2.0.1.4

41/65

Suppression of psoriasis after treatment  
with oligonucleotide (quantification)

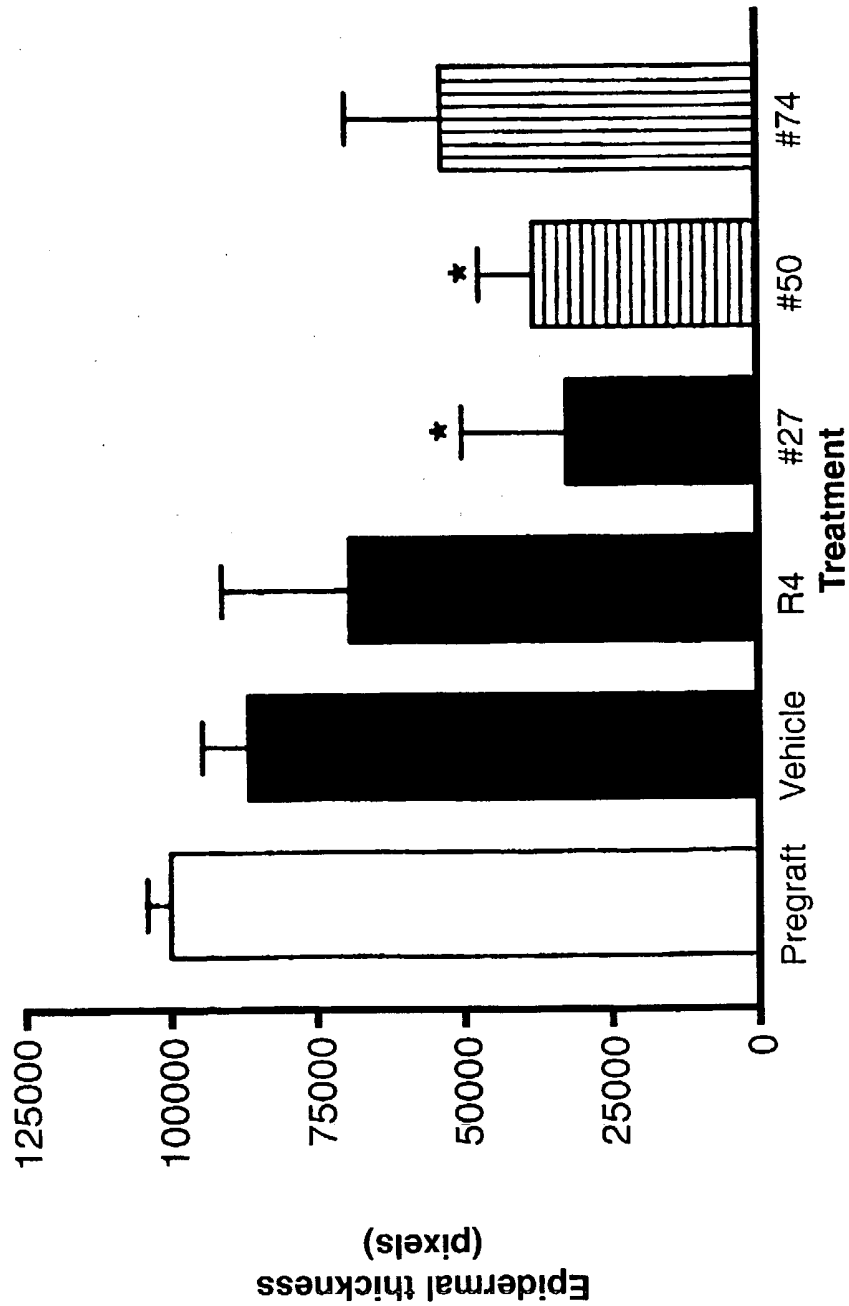
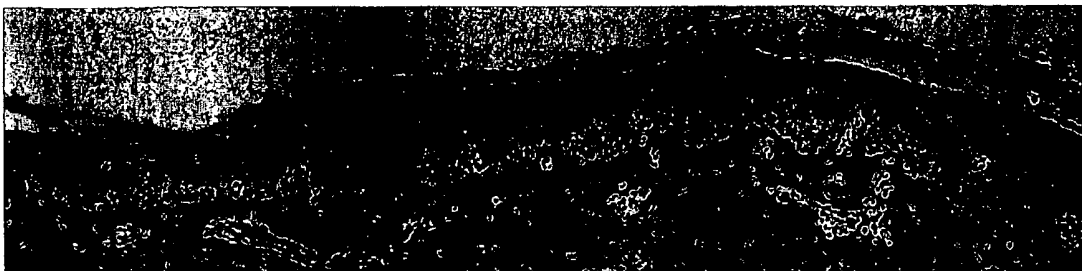


Figure 20

42/65

$\alpha$ hKi-67



Pregraft  
GM



Oligo 27

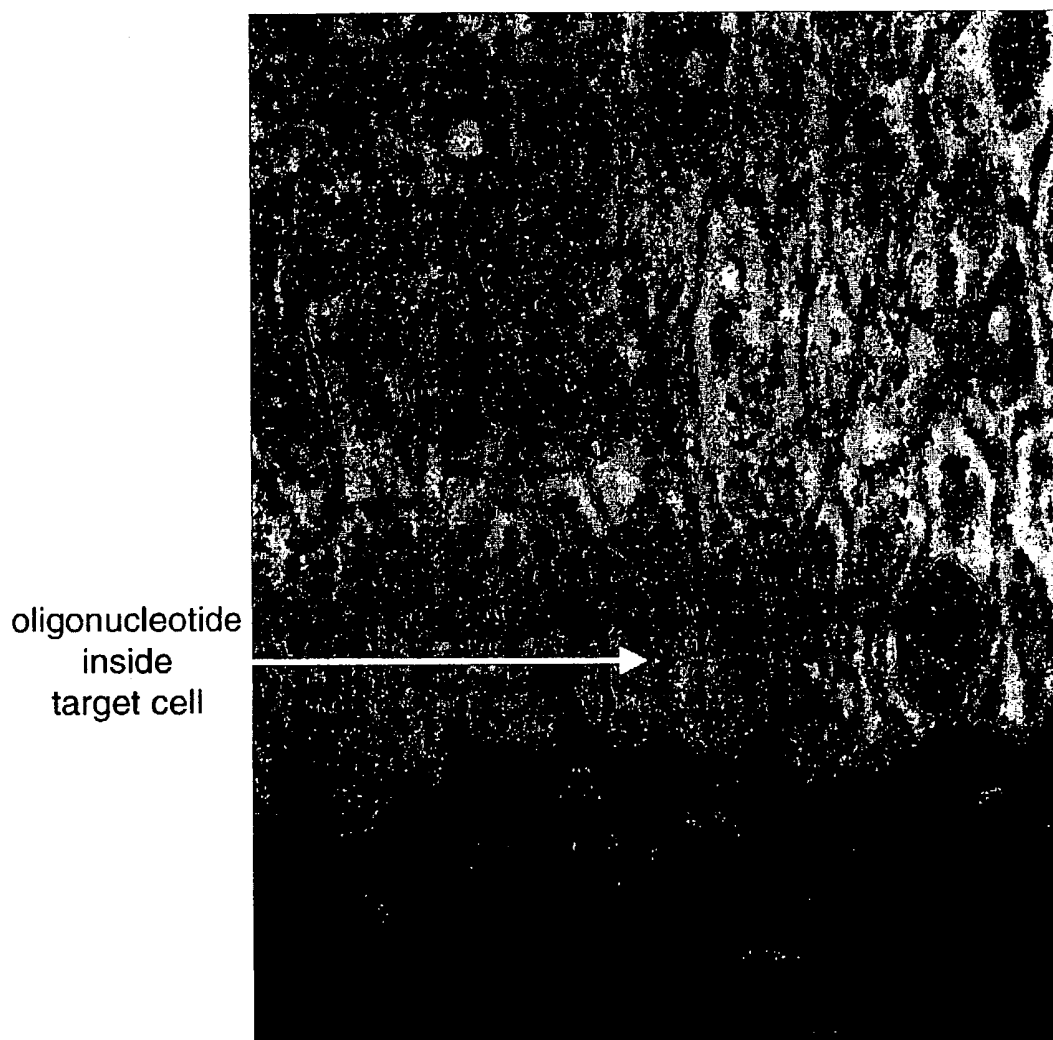


Oligo R451

Figure 21  
Substitute Sheet  
(Rule 26) RO/AU

43/65

# **Penetration of oligonucleotide into human skin after topical treatment**



**Figure 22**

Substitute Sheet  
(Rule 26) RO/AU

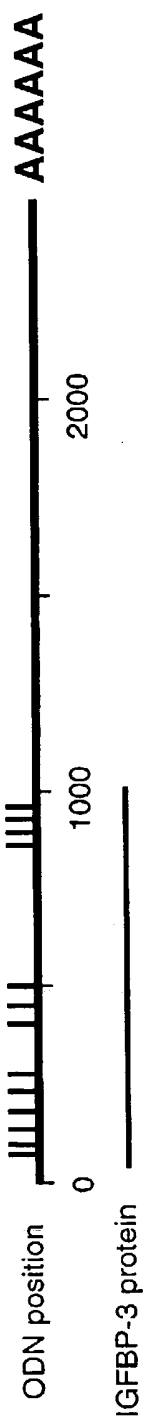
44/65

Penetration of oligonucleotide into human  
skin after topical gel formulation



Figure 23  
Substitute Sheet  
(Rule 26) RO/AU

45/65

**IGFBP-3 mRNA**

- Position of the 13 tested ODNs (I)
- mRNA transcript length = 2.5 Kb
- coding sequence 133-1009

**Figure 24**



46/65

IGFBP-3 mRNA in AON treated (100nM) HaCaT cells (2ug/ml GSV)

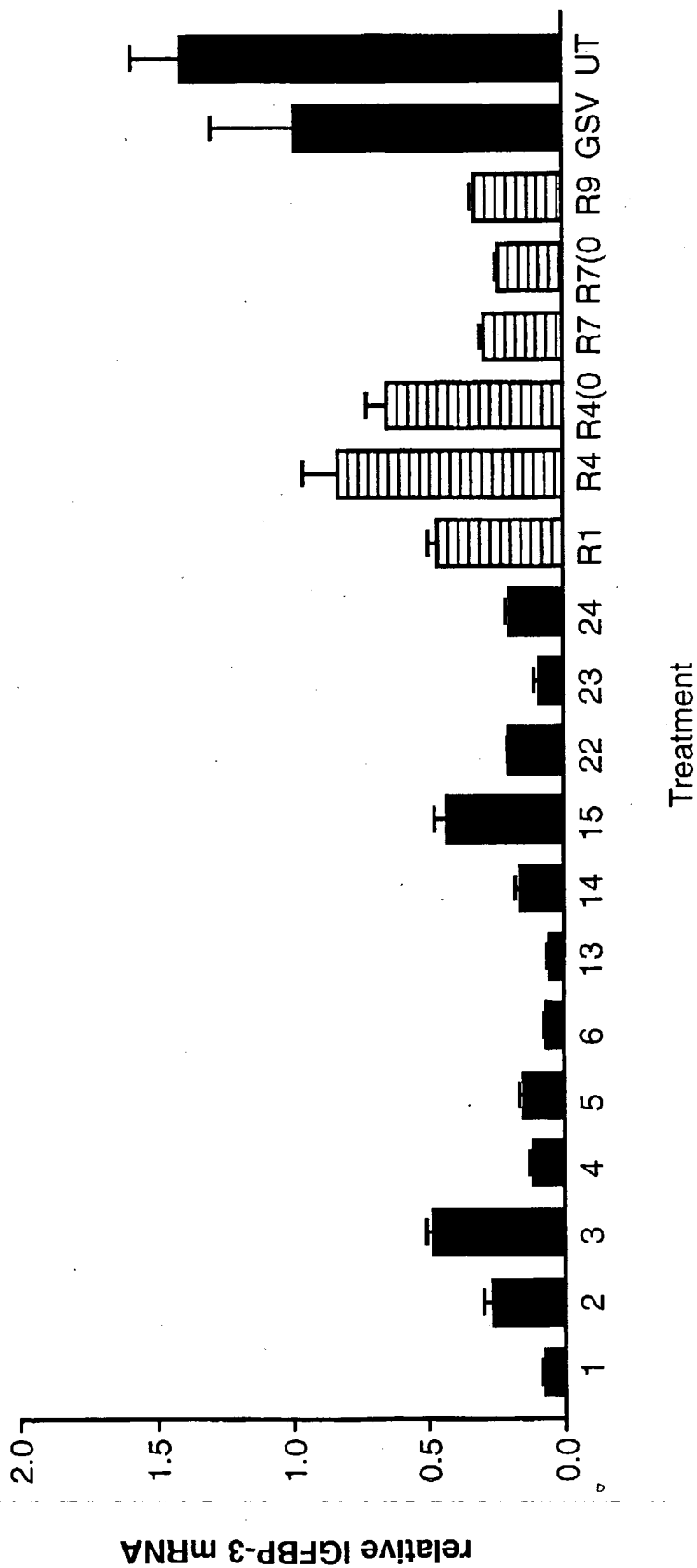


Figure 25a

47/65

IGFBP-3 mRNA levels in AON treated (100nM) HaCaT cells (2ug/ml GSV)

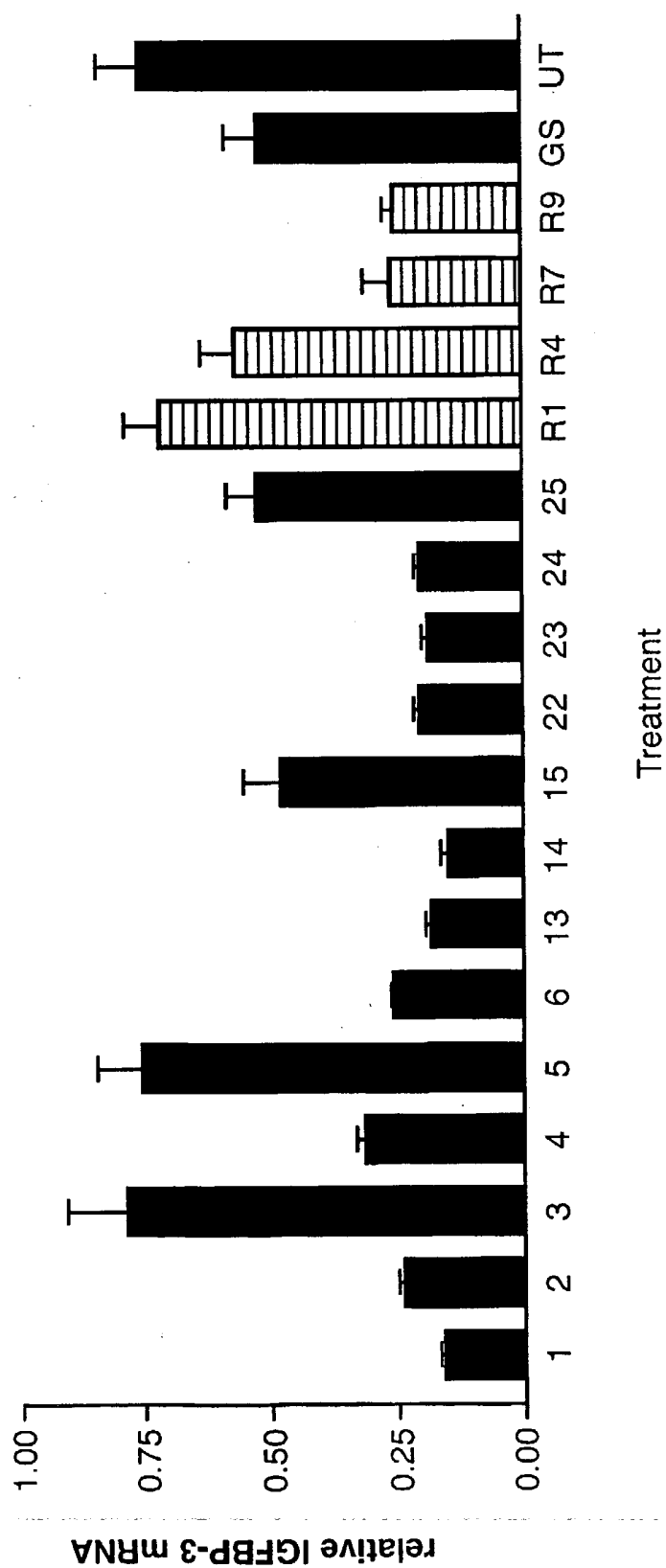


Figure 25b

IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2ug/ml GSV)

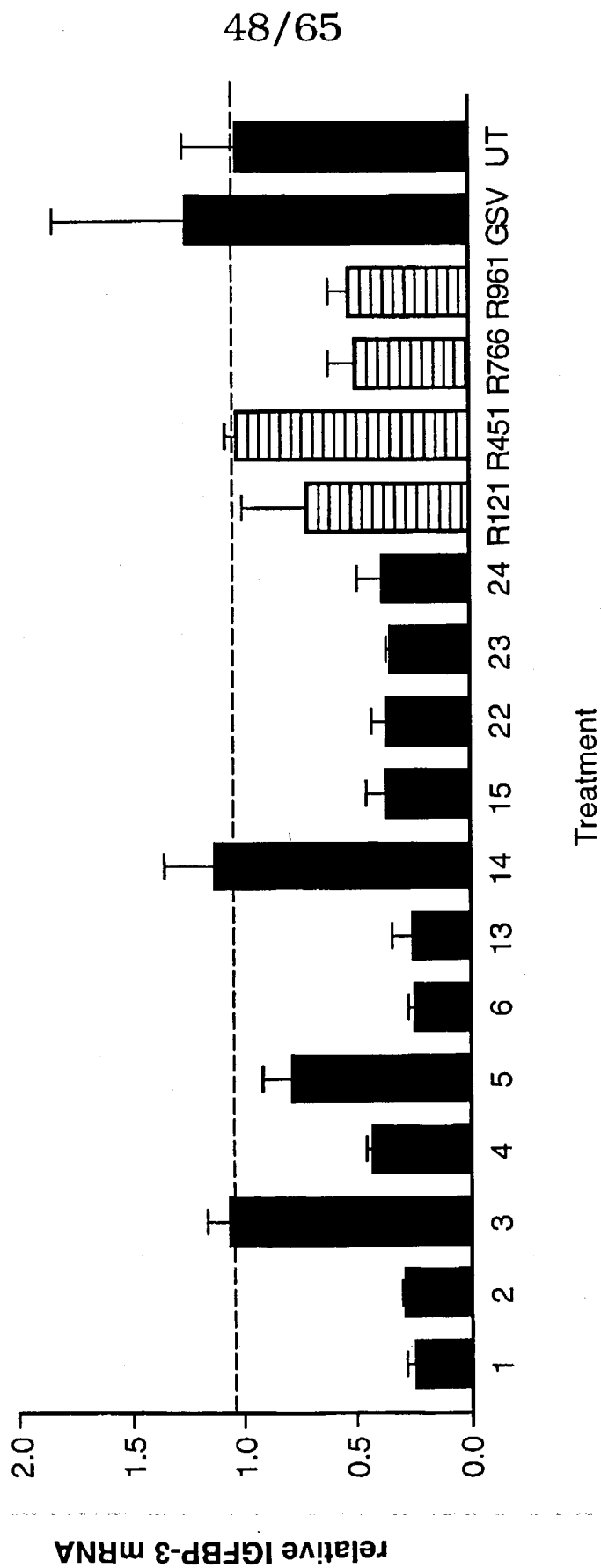


Figure 25c

49/65

IGFBP-3 mRNA in AON treated (30nM) HaCaT cells (2µg/ml GSV)

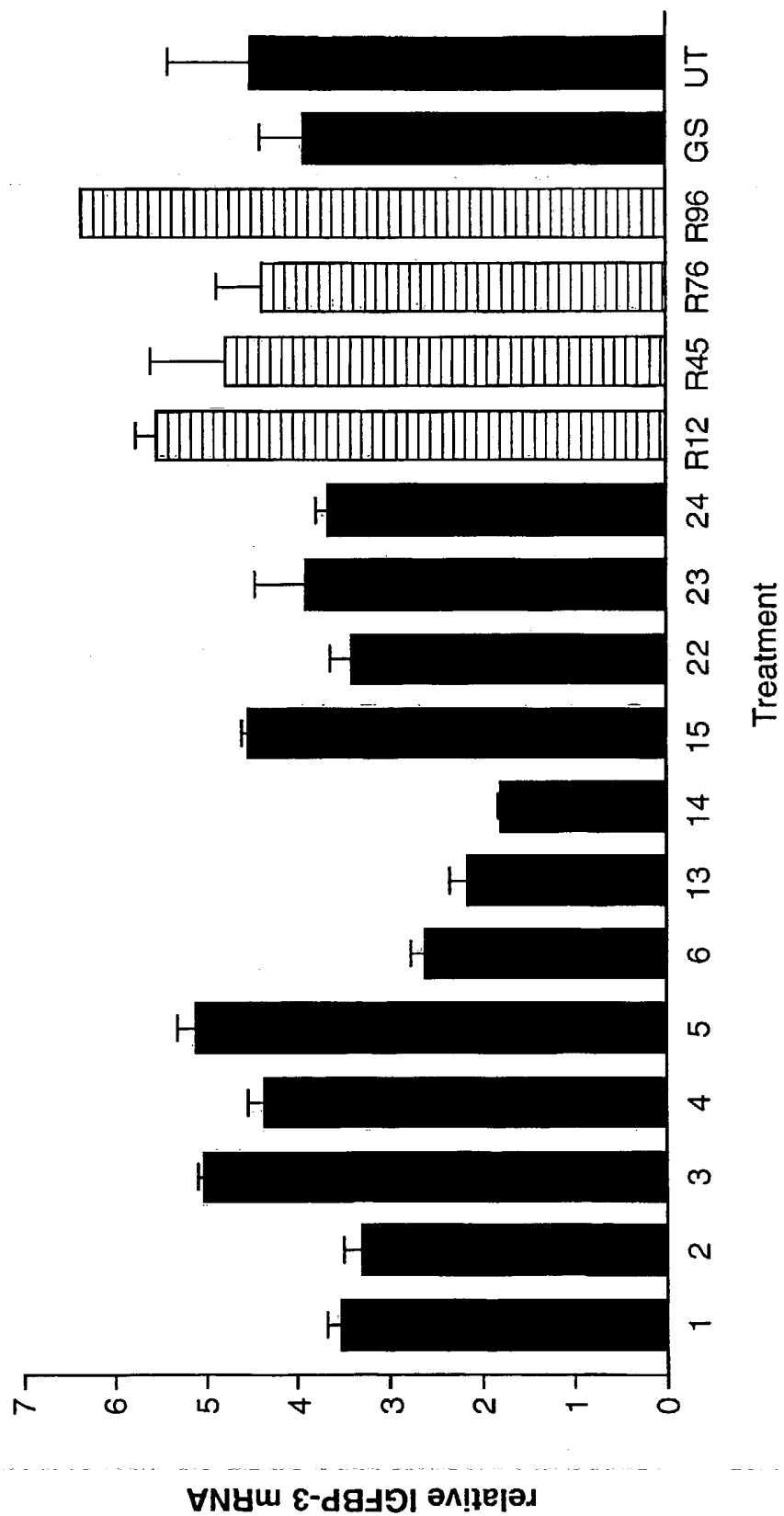


Figure 25d

50/65

IGFBP-3 mRNA in ODN treated (30nM) HaCaT cells (2µg/ml)

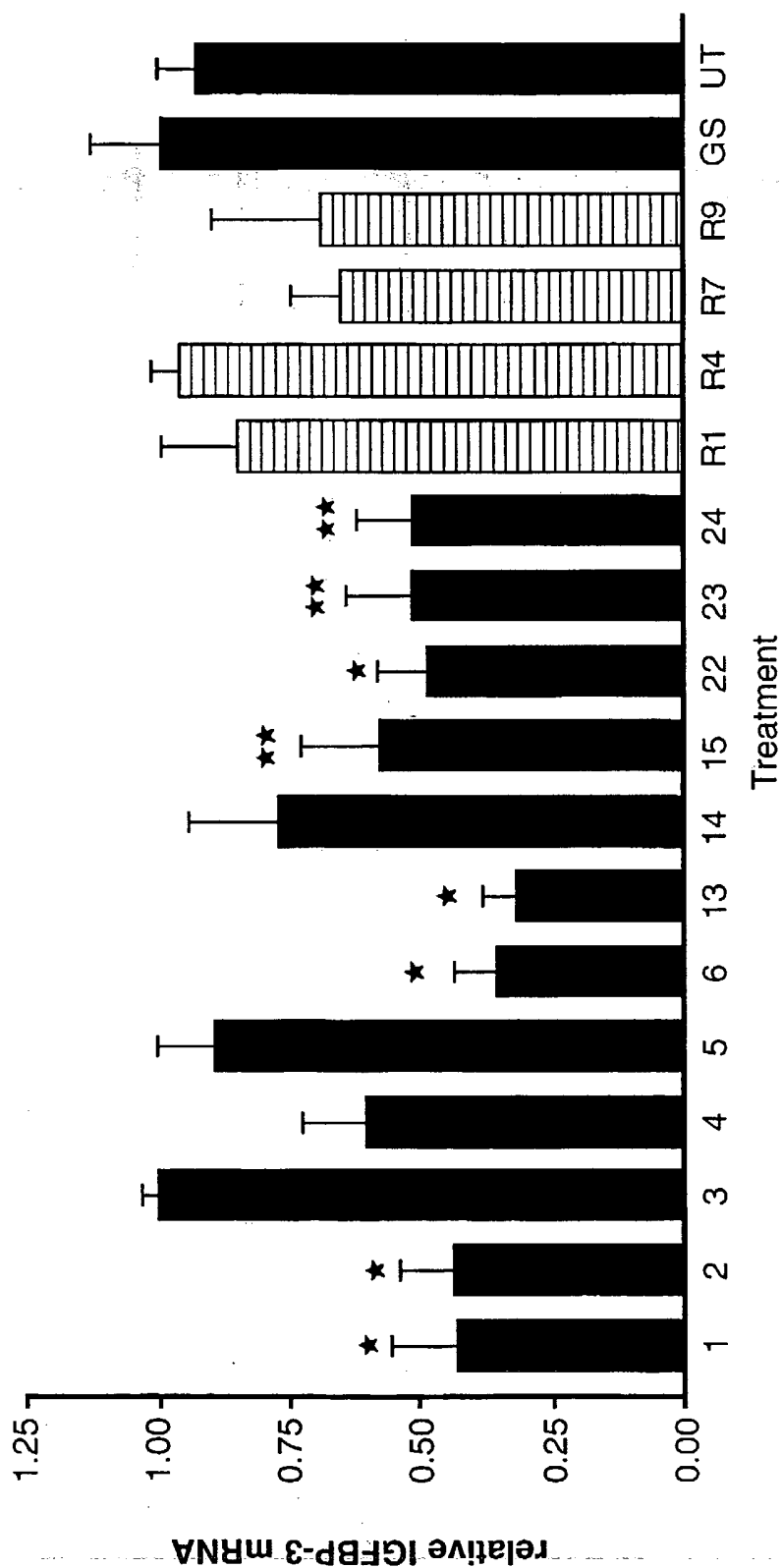


Figure 26a

51/65

IGFBP-3 mRNA in ODN treated (100nM) HaCaT cells (2µg/ml GSV)

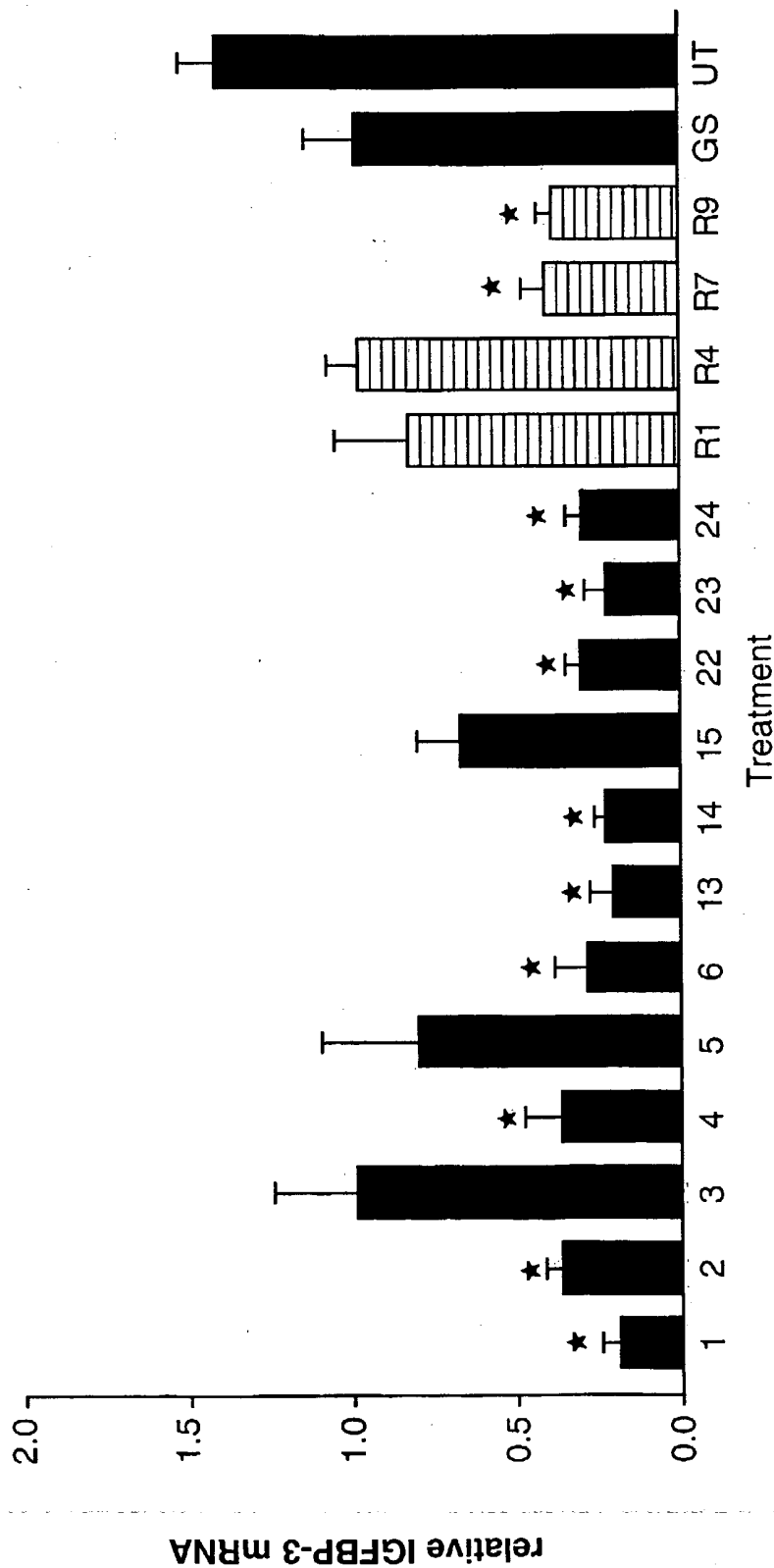


Figure 26b

52/65

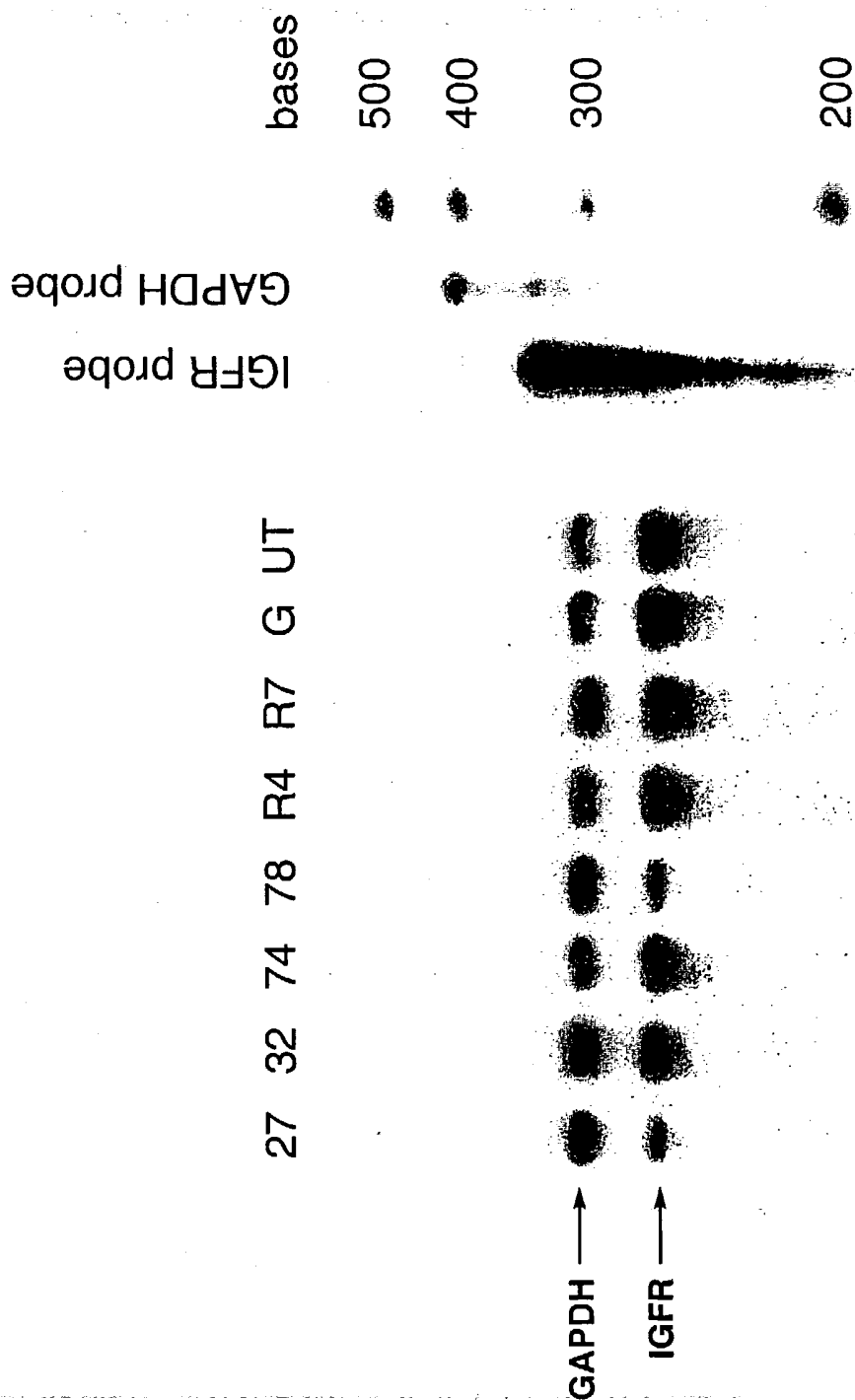


Figure 27a

53/65

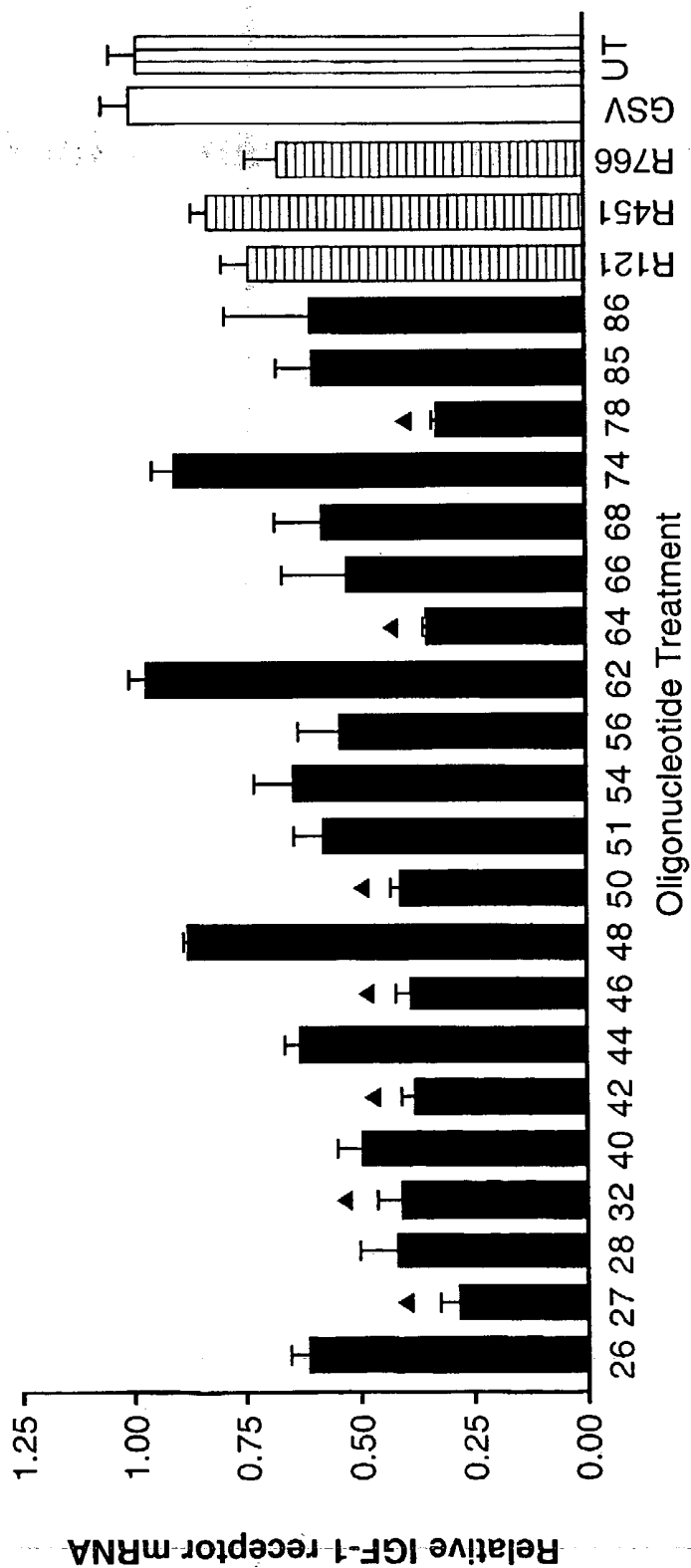


Figure 27 b



54/65

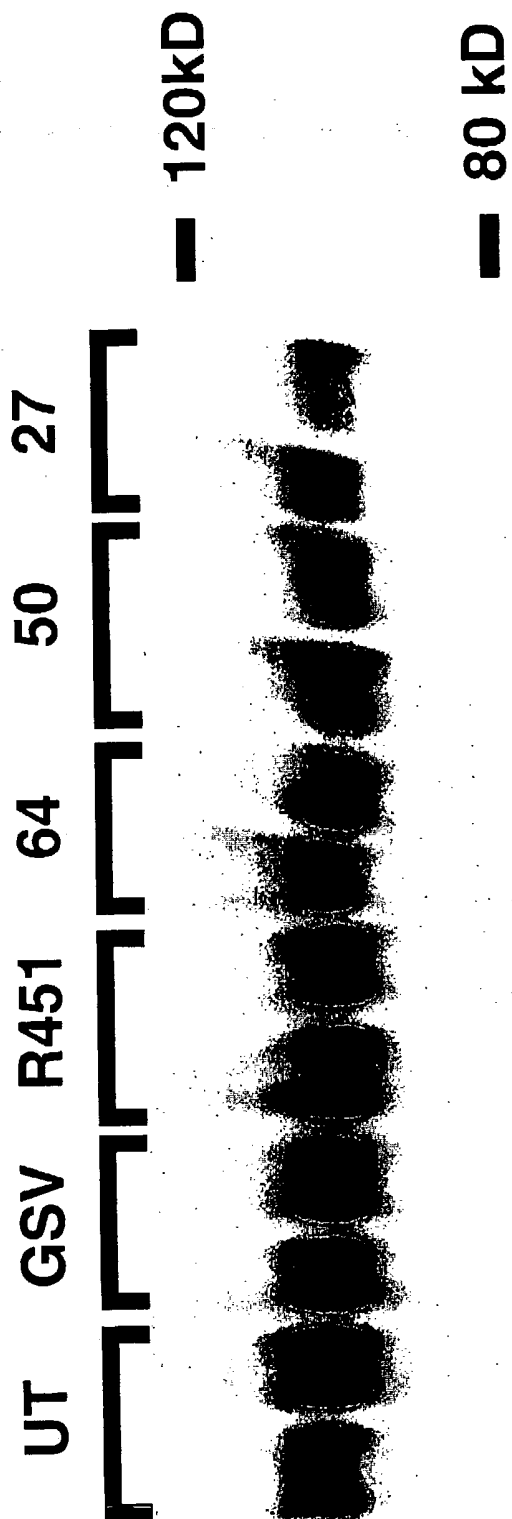


Figure 28a

55/65

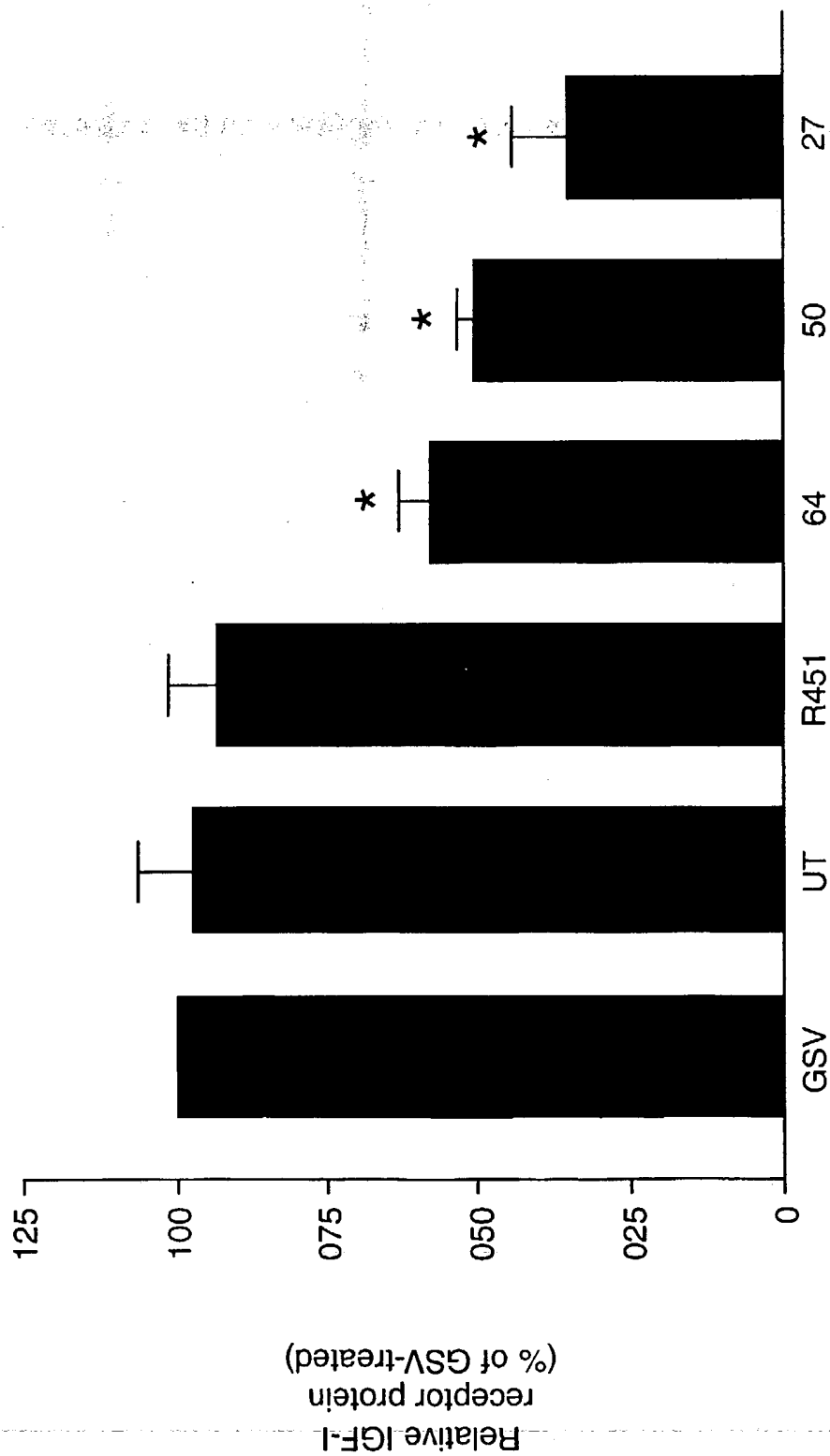


Figure 28b

56/65

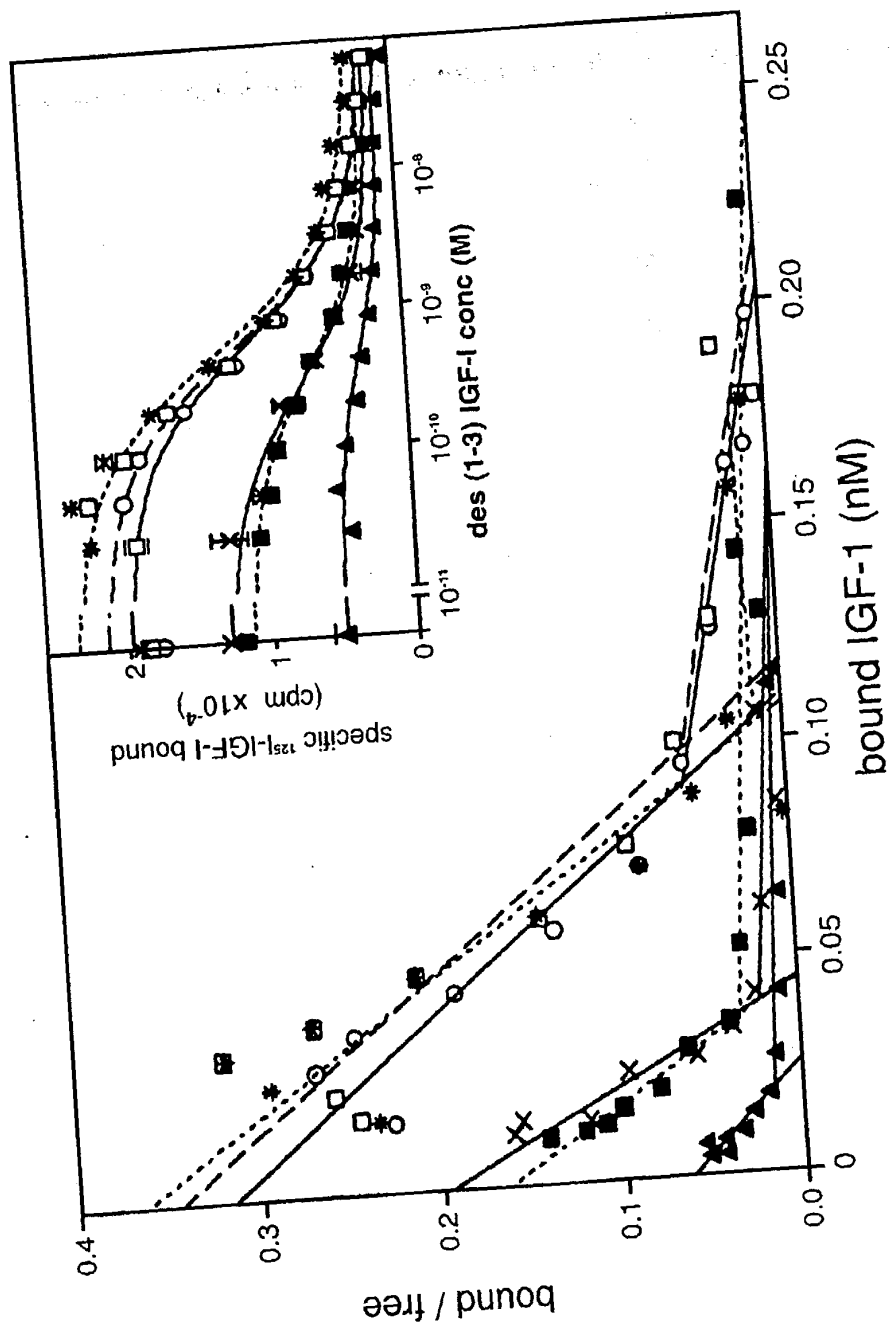


Figure 29

Substitute Sheet  
(Rule 26) RO/AU

57/65

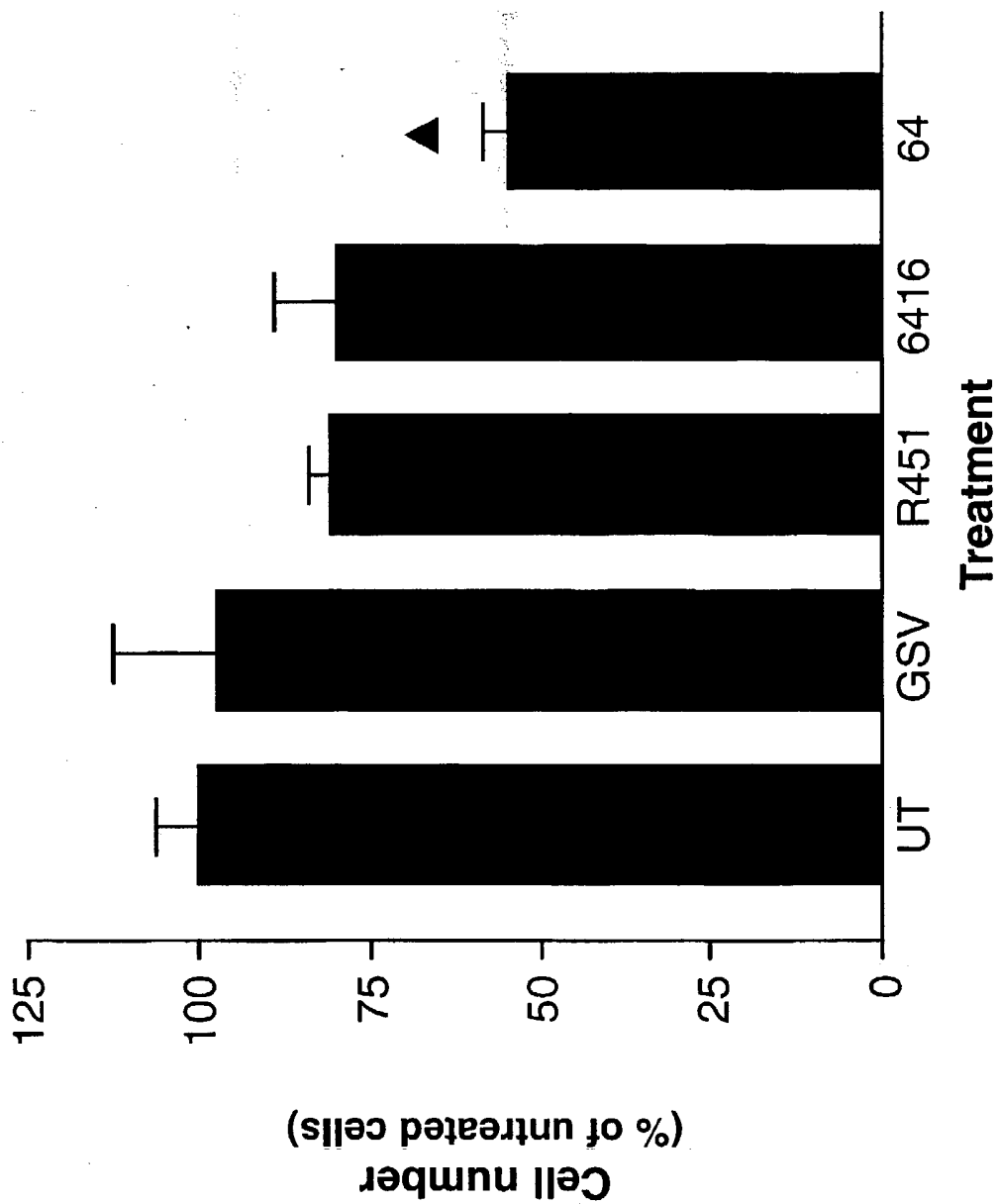


Figure 30

58/65

**DONOR B**



pregraft



AON #27



R451

**DONOR A**



pregraft



AON #50



PBS

Figure 31a

59/65

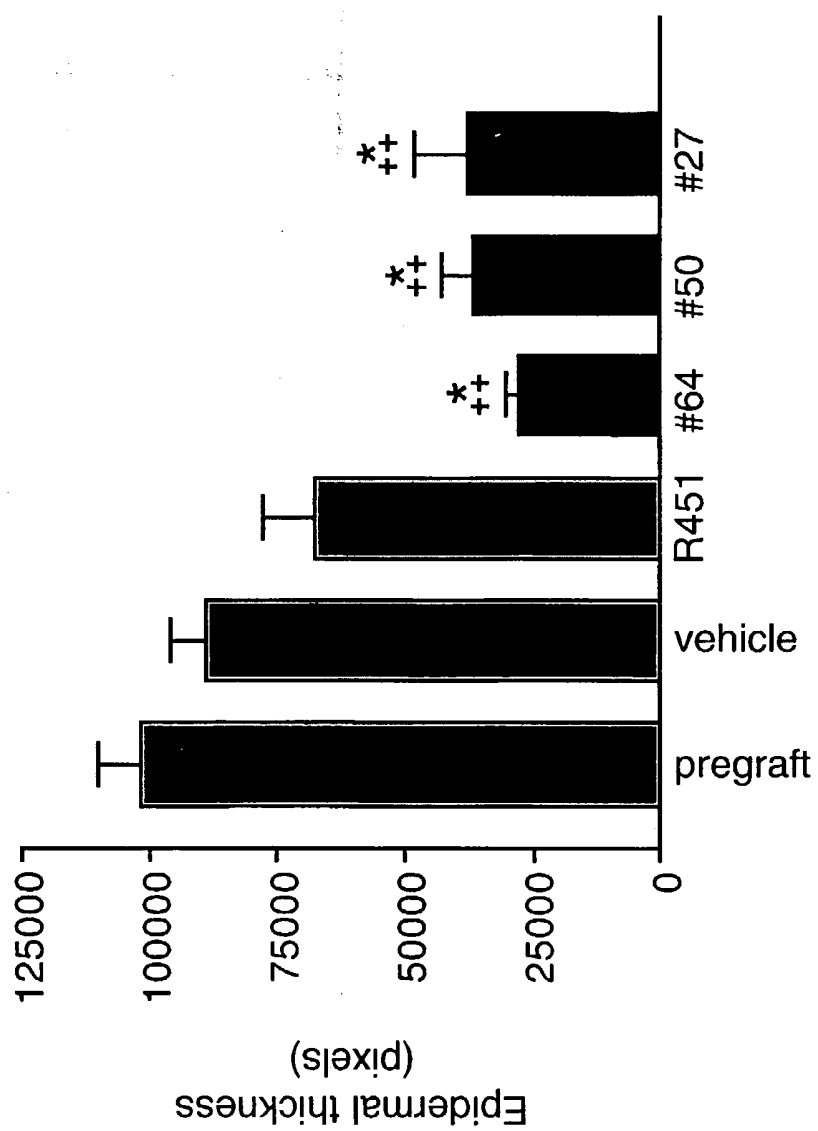


Figure 31b

60/65

**pregraft**



**AON #50**



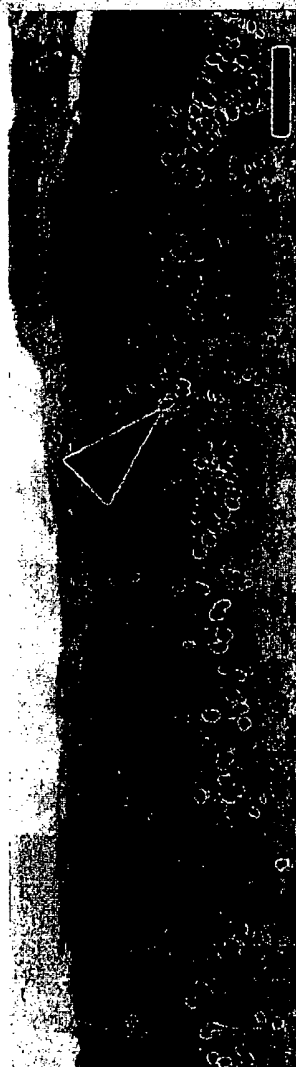
**PBS**



**Figure 31c**

Substitute Sheet  
(Rule 26) RO/AU

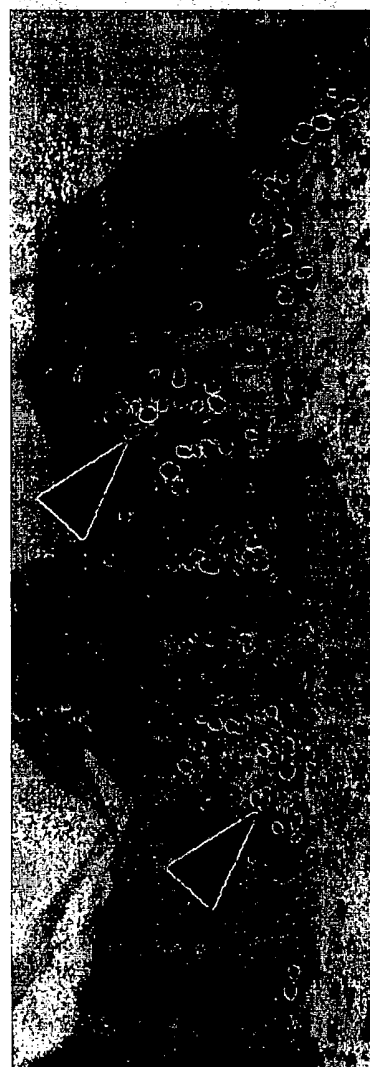
61/65



pregraft



AON #27



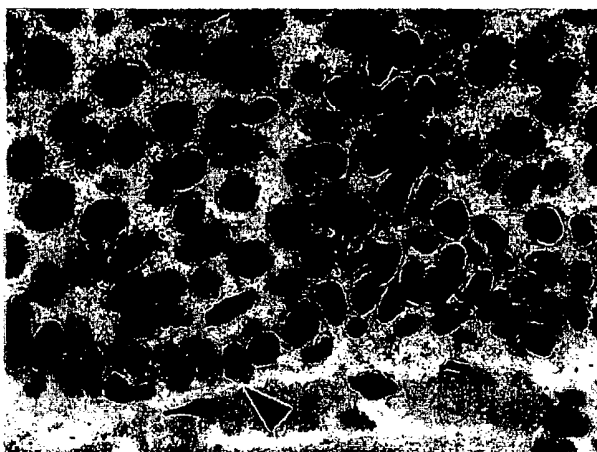
R451

Figure 32a



62/65

pregraft



AON #27



R451

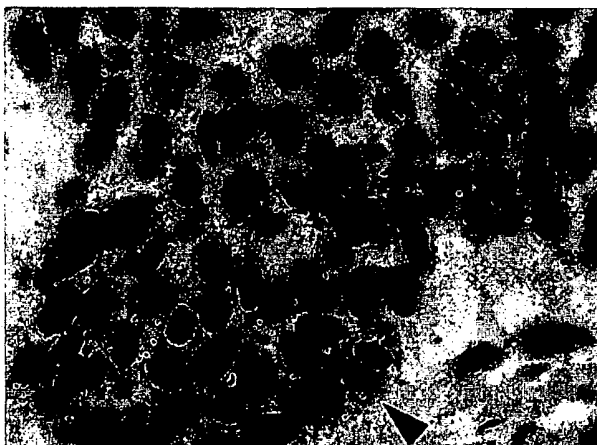


Figure 32b

Substitute Sheet  
(Rule 26) RO/AU

1/3/05, EAST Version: 2.0.1.4

63/65

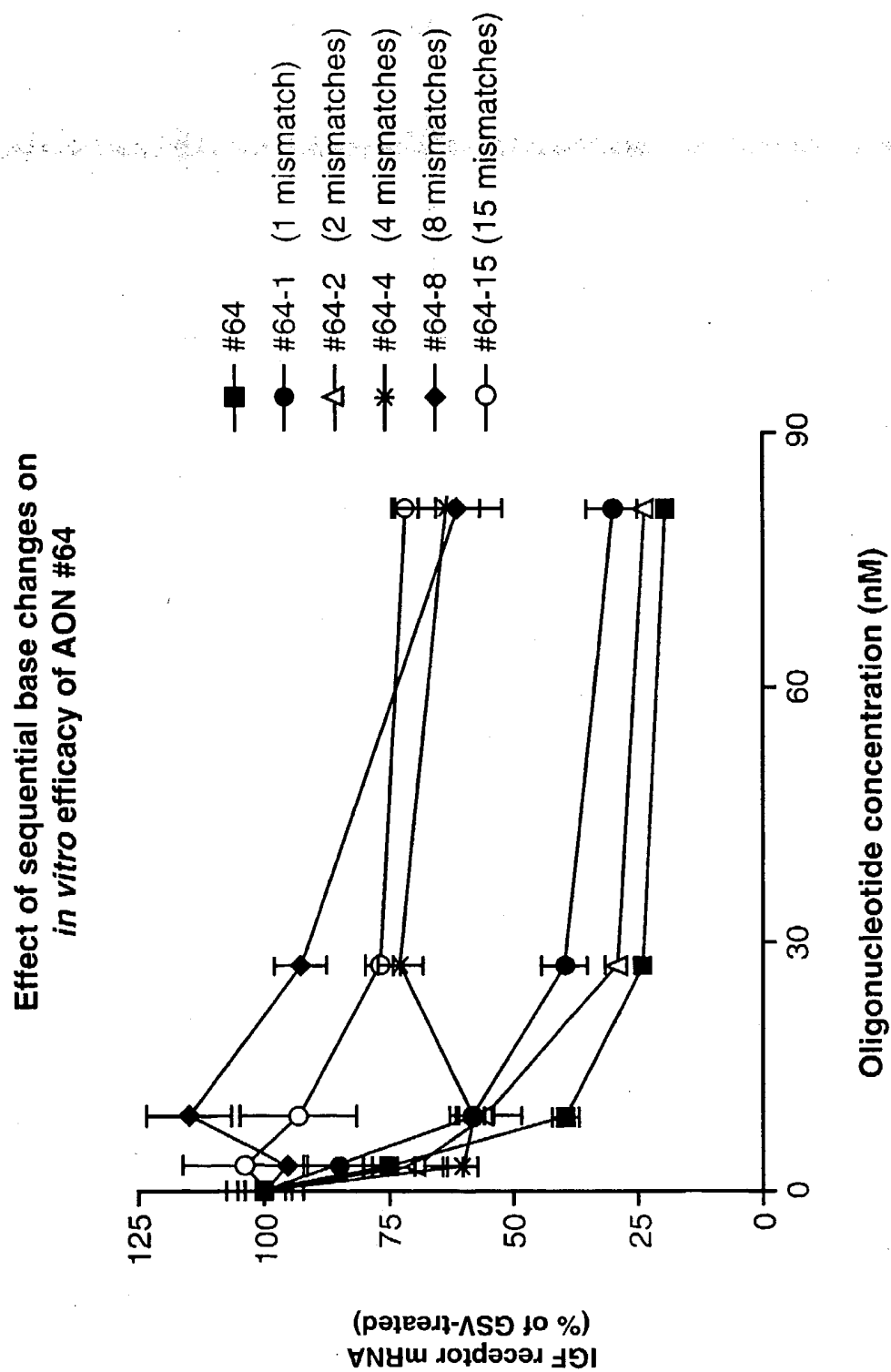


Figure 33

64/65

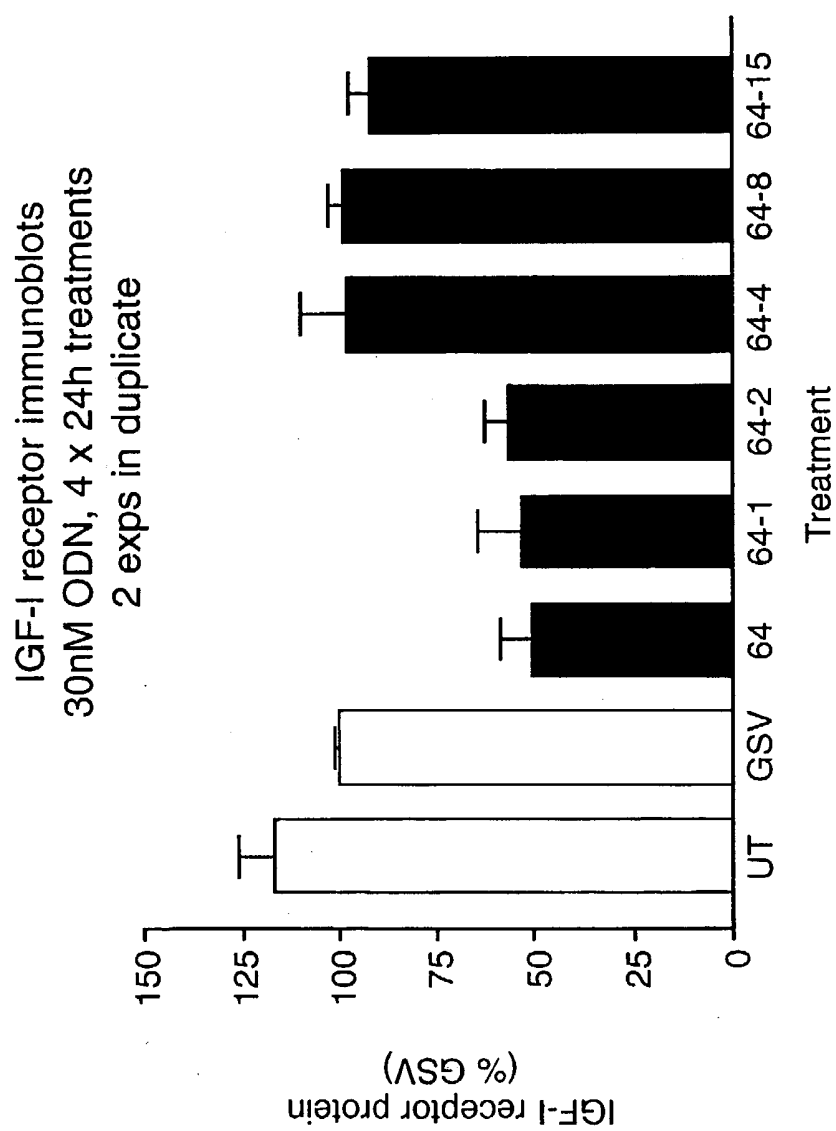


Figure 34

65/65

Amido black assay - 3 x 24h  
treatments (15nM ODN, 2ug/ml GSV)

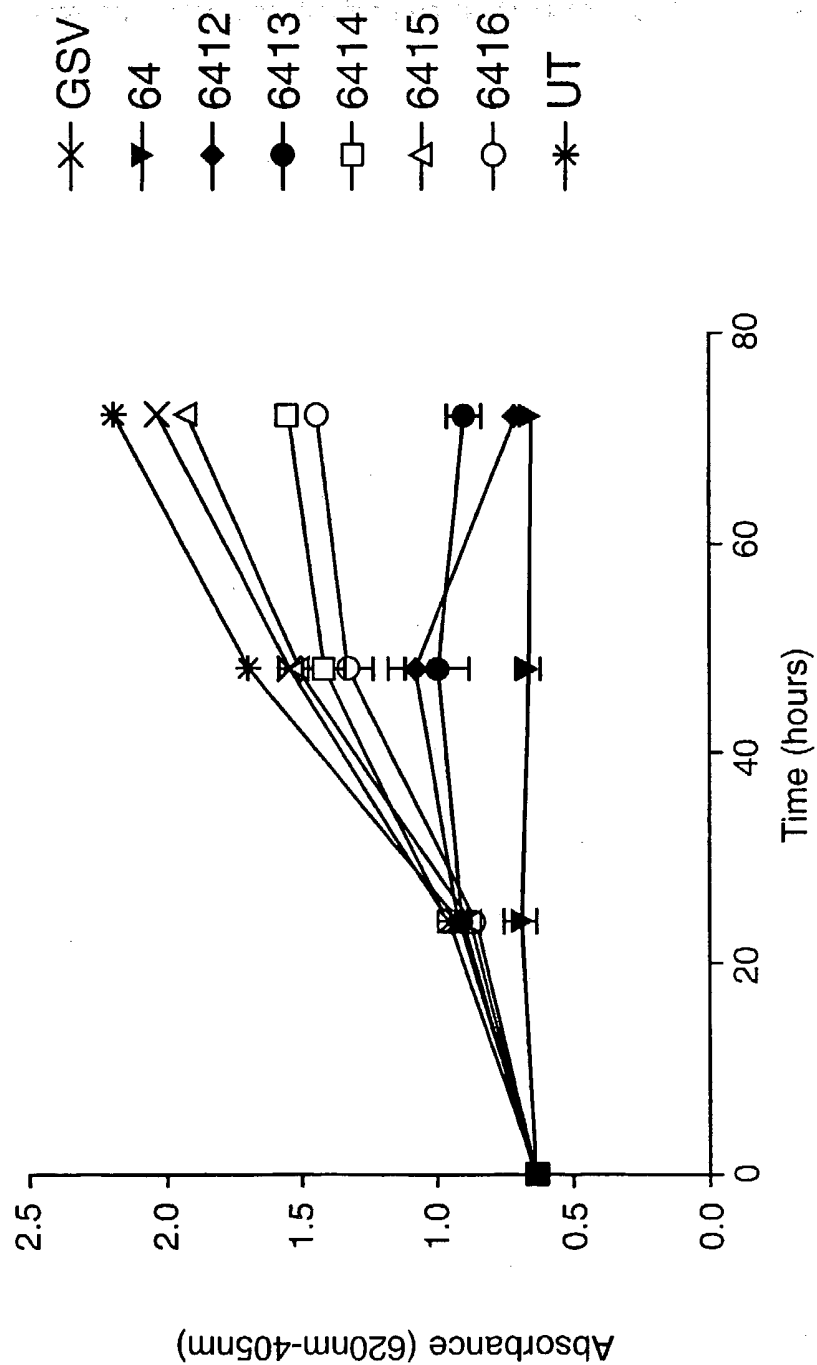


Figure 35

- 1 -

## SEQUENCE LISTING

&lt;110&gt; MURDOCH CHILDREN'S RESEARCH INSTITUTE

<120> A METHOD FOR THE PROPHYLAXIS AND/OR TREATMENT OF  
MEDICAL DISORDERS

&lt;130&gt; 2288267/EJH

&lt;140&gt; INTERNATIONAL

&lt;141&gt; 2000-06-21

&lt;150&gt; 60/140345

&lt;151&gt; 1999-06-21

&lt;160&gt; 24

&lt;170&gt; PatentIn Ver. 2.1

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&lt;212&gt; DNA

&lt;213&gt; synthetic construct

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- 2 -

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&lt;210&gt; 2

&lt;211&gt; 2474

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 2

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- 3 -

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&lt;210&gt; 3

&lt;211&gt; 4989

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 3

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- 4 -

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- 5 -

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&lt;211&gt; 25

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 4

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25

&lt;210&gt; -5

&lt;211&gt; 24

- 6 -

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 5

cgggcggtc acctggagct ggcg

24

&lt;210&gt; 6

&lt;211&gt; 18

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 6

aggcggtga cggcacta

18

&lt;210&gt; 7

&lt;211&gt; 19

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 7

caggcgatcat gcagcgggc

19

&lt;210&gt; 8

&lt;211&gt; 25

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 8

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25

&lt;210&gt; 9

&lt;211&gt; 18

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 9

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- 7 -

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&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 10

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18

&lt;210&gt; 11

&lt;211&gt; 18

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 11

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18

&lt;210&gt; 12

&lt;211&gt; 12

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 12

ccggagccag ac

12

&lt;210&gt; 13

&lt;211&gt; 12

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 13

cacaggcgca ag

12

&lt;210&gt; 14

&lt;211&gt; 8

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

- 8 -

&lt;400&gt; 14

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8

&lt;210&gt; 15

&lt;211&gt; 15

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 15

agccccca ggcgag

15

&lt;210&gt; 16

&lt;211&gt; 12

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 16

gccggagaga gc

12

&lt;210&gt; 17

&lt;211&gt; 13

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 17

aacagaggca gca

13

&lt;210&gt; 18

&lt;211&gt; 13

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 18

ggacaggac cag

13

&lt;210&gt; 19

- 9 -

&lt;211&gt; 14

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 19

cggcaagcac acag

14

&lt;210&gt; 20

&lt;211&gt; 15

&lt;212&gt; DNA

&lt;213&gt; synthetic construct

&lt;400&gt; 20

ggcaggcagg cacac

15

&lt;210&gt; 21

&lt;211&gt; 328

&lt;212&gt; PRT

&lt;213&gt; human

&lt;400&gt; 21

Met Leu Pro Arg Val Gly Cys Pro Ala Leu Pro Leu Pro Pro Pro Pro

1

5

10

15

Leu Leu Pro Leu Leu Pro Leu Leu Leu Leu Leu Gly Ala Ser Gly

20

25

30

Gly Gly Gly Gly Ala Arg Ala Glu Val Leu Phe Arg Cys Pro Pro Cys

35

40

45

Thr Pro Glu Arg Leu Ala Ala Cys Gly Pro Pro Pro Val Ala Pro Pro

50

55

60

Ala Ala Val Ala Ala Val Ala Gly Gly Ala Arg Met Pro Cys Ala Glu

65

70

75

80

Leu Val Arg Glu Pro Gly Cys Gly Cys Cys Ser Val Cys Ala Arg Leu

85

90

95

- 10 -

Glu Gly Glu Ala Cys Gly Val Tyr Thr Pro Arg Cys Gly Gln Gly Leu  
 100 105 110

Arg Cys Tyr Pro His Pro Gly Ser Glu Leu Pro Leu Gln Ala Leu Val  
 115 120 125

Met Gly Glu Gly Thr Cys Glu Lys Arg Arg Asp Ala Glu Tyr Gly Ala  
 130 135 140

Ser Pro Glu Gln Val Ala Asp Asn Gly Asp Asp His Ser Glu Gly Gly  
 145 150 155 160

Leu Val Glu Asn His Val Asp Ser Thr Met Asn Met Leu Gly Gly Gly  
 165 170 175

Gly Ser Ala Gly Arg Lys Pro Leu Lys Ser Gly Met Lys Glu Leu Ala  
 180 185 190

Val Phe Arg Glu Lys Val Thr Glu Gln His Arg Gln Met Gly Lys Gly  
 195 200 205

Gly Lys His His Leu Gly Leu Glu Glu Pro Lys Lys Leu Arg Pro Pro  
 210 215 220

Pro Ala Arg Thr Pro Cys Gln Gln Glu Leu Asp Gln Val Leu Glu Arg  
 225 230 235 240

Ile Ser Thr Met Arg Leu Pro Asp Glu Arg Gly Pro Leu Glu His Leu  
 245 250 255

Tyr Ser Leu His Ile Pro Asn Cys Asp Lys His Gly Leu Tyr Asn Leu  
 260 265 270

Lys Gln Cys Lys Met Ser Leu Asn Gly Gln Arg Gly Glu Cys Trp Cys  
 275 280 285

Val Asn Pro Asn Thr Gly Lys Leu Ile Gln Gly Ala Pro Thr Ile Arg  
 290 295 300

Gly Asp Pro Glu Cys His Leu Phe Tyr Asn Glu Gln Gln Glu Ala Cys  
 305 310 315 320

- 11 -

Gly Val His Thr Gln Arg Met Gln

325

&lt;210&gt; 22

&lt;211&gt; 39

&lt;212&gt; PRT

&lt;213&gt; human

&lt;400&gt; 22

Met Leu Pro Arg Val Gly Cys Pro Ala Leu Pro Leu Pro Pro Pro Pro

1

5

10

15

Leu Leu Pro Leu Leu Pro Leu Leu Leu Leu Leu Leu Gly Ala Ser Gly

20

25

30

Gly Gly Gly Gly Ala Arg Ala

35

&lt;210&gt; 23

&lt;211&gt; 289

&lt;212&gt; PRT

&lt;213&gt; human

&lt;400&gt; 23

Glu Val Leu Phe Arg Cys Pro Pro Cys Thr Pro Glu Arg Leu Ala Ala

1

5

10

15

Cys Gly Pro Pro Pro Val Ala Pro Pro Ala Ala Val Ala Ala Val Ala

20

25

30

Gly Gly Ala Arg Met Pro Cys Ala Glu<sup>n</sup> Leu Val Arg Glu Pro Gly Cys

35

40

45

Gly Cys Cys Ser Val Cys Ala Arg Leu Glu Gly Glu Ala Cys Gly Val

50

55

60

Tyr Thr Pro Arg Cys Gly Gln Gly Leu Arg Cys Tyr Pro His Pro Gly

65

70

75

80

- 12 -

Ser Glu Leu Pro Leu Gln Ala Leu Val Met Gly Glu Gly Thr Cys Glu  
85 90 95

Lys Arg Arg Asp Ala Glu Tyr Gly Ala Ser Pro Glu Gln Val Ala Asp  
100 105 110

Asn Gly Asp Asp His Ser Glu Gly Gly Leu Val Glu Asn His Val Asp  
115 120 125

Ser Thr Met Asn Met Leu Gly Gly Gly Gly Ser Ala Gly Arg Lys Pro  
130 135 140

Leu Lys Ser Gly Met Lys Glu Leu Ala Val Phe Arg Glu Lys Val Thr  
145 150 155 160

Glu Gln His Arg Gln Met Gly Lys Gly Gly Lys His His Leu Gly Leu  
165 170 175

Glu Glu Pro Lys Lys Leu Arg Pro Pro Pro Ala Arg Thr Pro Cys Gln  
180 185 190

Gln Glu Leu Asp Gln Val Leu Glu Arg Ile Ser Thr Met Arg Leu Pro  
195 200 205

Asp Glu Arg Gly Pro Leu Glu His Leu Tyr Ser Leu His Ile Pro Asn  
210 215 220

Cys Asp Lys His Gly Leu Tyr Asn Leu Lys Gln Cys Lys Met Ser Leu  
225 230 235 240

Asn Gly Gln Arg Gly Glu Cys Trp Cys Val Asn Pro Asn Thr Gly Lys  
245 250 255

Leu Ile Gln Gly Ala Pro Thr Ile Arg Gly Asp Pro Glu Cys His Leu  
260 265 270

Phe Tyr Asn Glu Gln Gln Glu Ala Cys Gly Val His Thr Gln Arg Met  
275 280 285

Gln



- 13 -

&lt;210&gt; 24

&lt;211&gt; 291

&lt;212&gt; PRT

&lt;213&gt; human

&lt;400&gt; 24

Met Gln Arg Ala Arg Pro Thr Leu Trp Ala Ala Ala Leu Thr Leu Leu  
 1 5 10 15

Val Leu Leu Arg Gly Pro Pro Val Ala Arg Ala Gly Ala Ser Ser Gly  
 20 25 30

Gly Leu Gly Pro Val Val Arg Cys Glu Pro Cys Asp Ala Arg Ala Leu  
 35 40 45

Ala Gln Cys Ala Pro Pro Pro Ala Val Cys Ala Glu Leu Val Arg Glu  
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Pro Gly Cys Gly Cys Cys Leu Thr Cys Ala Leu Ser Glu Gly Gln Pro  
 65 70 75 80

Cys Gly Ile Tyr Thr Glu Arg Cys Gly Ser Gly Leu Arg Cys Gln Pro  
 85 90 95

Ser Pro Asp Glu Ala Arg Pro Leu Gln Ala Leu Leu Asp Gly Arg Gly  
 100 105 110

Leu Cys Val Asn Ala Ser Ala Val Ser Arg Leu Arg Ala Tyr Leu Leu  
 115 120 125

Pro Ala Pro Pro Ala Pro Gly Asn Ala Ser Glu Ser Glu Glu Asp Arg  
 130 135 140

Ser Ala Gly Ser Val Glu Ser Pro Ser Val Ser Ser Thr His Arg Val  
 145 150 155 160

Ser Asp Pro Lys Phe His Pro Leu His Ser Lys Ile Ile Ile Ile Lys  
 165 170 175

Lys Gly His Ala Lys Asp Ser Gln Arg Tyr Lys Val Asp Tyr Glu Ser

- 14 -

180	185	190
Gln Ser Thr Asp Thr Gln Asn Phe Ser Ser Glu Ser Lys Arg Glu Thr		
195	200	205
Glu Tyr Gly Pro Cys Arg Arg Glu Met Glu Asp Thr Leu Asn His Leu		
210	215	220
Lys Phe Leu Asn Val Leu Ser Pro Arg Gly Val His Ile Pro Asn Cys		
225	230	235 240
Asp Lys Lys Gly Phe Tyr Lys Lys Lys Gln Cys Arg Pro Ser Lys Gly		
245	250	255
Arg Lys Arg Gly Phe Cys Trp Cys Val Asp Lys Tyr Gly Gln Pro Leu		
260	265	270
Pro Gly Tyr Thr Thr Lys Gly Lys Glu Asp Val His Cys Tyr Ser Met		
275	280	285
Gln Ser Lys		
290		

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 00/00693

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>												
Int Cl <sup>7</sup> : A61K 38/30; 17/06; 17/02												
According to International Patent Classification (IPC) or to both national classification and IPC												
<b>B. FIELDS SEARCHED</b>												
Minimum documentation searched (classification system followed by classification symbols)												
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched												
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Derwent WPAT IGF-1, IGFBP, Insulin Like Growth Factor/Binding Pair.												
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>												
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
Y	AU 77314/94,A (688793) (Celtrix Pharmaceuticals, Inc.) 30 March 1995.	1-9, 20-22, 25, 29-37										
X	AU 28753/95,A (692278) (Royal Children's Hospital Research Foundation, Australia.) 25 January 1996.	1-13, 20-23, 29-36										
X	Wraight, Christopher J. et al., Expression of insulin-like growth factor binding protein-3 (IGFBP-3) J. Invest. Dermatol. (1997), 108(4), 452-456.	1-13,20-23,29-36										
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input type="checkbox"/> See patent family annex												
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" Document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&amp;" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" Document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed	
"A" Document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention											
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone											
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art											
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family											
"P" document published prior to the international filing date but later than the priority date claimed												
Date of the actual completion of the international search 24 August 2000		Date of mailing of the international search report - 4 OCT 2000										
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustalia.gov.au Facsimile No.: (02) 6285 3929		Authorized officer  A. WILCOX Telephone No.: (02) 6283 2243										

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 00/00693

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Jeschke, Marc G.; Barrow, Robert E.; Hawkins, Hal K.; Chrysopoula, Mina S. T.; Perez-Polo, J. Regina; Herdon, David, N. Effect of Multiple gene transfers of insulin like growth factor I complementary DNA gene constructs in rats after thermal injury. Arch. Surg. (1999), 134(10), 1137-1141.	1-13,20-23,29-36
X	WO 96/01636 (Royal Childrens Hospital Research Foundation) 25 January 1996.	1-13
X	WO 96/33216 (Pharmacia AB) 24 October 1996.	1-13

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/AU 00/00693

**Box I** Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1,2,5-8 have been partially searched.  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
The specification provides support for methods and compositions which inhibit IGF-1 mediated cell proliferation and/or inflammation. There is no basis in the specification for methods and compositions derived from an invention for the treatment of cell proliferation and/or inflammation mediated by factors other than IGF-1.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box II** Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
The claims are directed to methods and compositions which inhibit IGF-1 mediated cell proliferation and/or inflammation. The broader claims include cell proliferation and/or inflammation mediated by keratinocyte growth factor (KGF), TGF- $\alpha$ , TNF- $\alpha$ , IL-1, IL-2, IL-6, IL-8 and/or basic fibroblast growth factor (bFGF). Claims 1,2 and 5-8 are considered to include multiple inventions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.